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Review Article

Brain, Diabetes and Cognition

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Abstract

Diabetes mellitus (DM) is a chronic metabolic disease, characterized mainly by elevated levels of blood glucose, associated with other important metabolic disturbances. Prevalence of DM is dramatically increasing worldwide, but especially in western countries, due to several factors as like diet, lifestyle and population aging.

Recent studies demonstrate that some diabetic patients have an increased risk of developing cognitive decline and dementia compared with healthy individuals. Although this may reflect brain changes as a consequence of diabetes, the coexistence of diabetes and cognitive dysfunction suggest common risk factors and causative mechanisms.

Cognitive dysfunction, including mild cognitive impairment and dementia, is increasingly recognized as an important comorbidity and complication of diabetes that affects patient's health and diabetes management with several public health implications. The aim of our work is to give an overview of cognitive dysfunction in people with diabetes, describing its clinical features and their biochemical basis and future perspectives.

Keywords: *Diabetes Mellitus (DM); Diet; Lifestyle; Population Aging*

Introduction

Diabetes Mellitus (DM) is increasing its prevalence in all the world, and especially in western countries reaching epidemic proportions due to a combination of several factors, as like dietary habits, sedentary lifestyle and aging population, among others. It configures a chronic metabolic disease and one of the most important public health challenges in the 21st century and becomes a major health and socioeconomic problem [38].

DM is broadly characterized by elevated levels of blood glucose, mainly caused by insufficient insulin production or diminished response of the body to insulin.

Some epidemiological data reveals the growing magnitude of the problem.

According to the latest data from the International Diabetes Federation there are 425 million people with diabetes in the world, and one in 11 adults worldwide is diagnosed as having DM. By 2045, the number of people with DM is expected to increase to 629 million. Recent epidemiological studies have shown that diabetic patients are more susceptible to cognitive compromise and decline than healthy individuals [1,2,10].

Following the World Health Organization (WHO), approximately 50 million people worldwide have dementia. Although there are different types of dementia, the most well-known form is Alzheimer's disease (AD), which accounts for 50% - 75% of all cases [3,6].

AD can damage cells and nerves interrupting the transmitters that convey information in the brain, particularly those responsible for memory storage. Generally, gradual memory loss is the first symptom of AD, but other signs include speech disorders, misidentification, temporal or geographic disorientation, and solving problems abilities, with marked repercussion and affection of the daily living activities. In addition, the majority of AD cases usually present multiple complications as like DM, other neurodegenerative disorders, cardiovascular diseases, and renal diseases. These comorbidities can enhance the complexity that underlies AD pathogenesis [5].

From the data of several epidemiological studies of AD in diabetic patients we can conclude that high AD prevalence in some diabetic populations may be related to insulin resistance and metabolic abnormalities. However, not all individuals with DM develop dementia, and not all dementia cases have DM. Diabetes in midlife is associated with a 19% greater cognitive decline over 20 years compared to those without diabetes [6].

A systematic review of 14 studies examined data from 2.3 million individuals and over 100,000 incident cases of dementia from cohorts from Asia, Europe, and the Americas. It was found that diabetes was significantly associated with an approximately 50% increased risk of dementia, compared with general population [47].

Diabetes mellitus is associated with alterations in cognitive function and changes in brain structure. People with both type 1 and type 2 diabetes have been shown to have mild to moderate reductions in cognitive function as compared to non-diabetic subjects [4,47].

Both type 1 (T1DM) and type 2 (T2DM) diabetes are associated with mild to moderate decrements in cognitive function. They are significant differences in the underlying pathophysiology of cognitive impairment between type 1 and type 2 diabetes. T1DM is usually diagnosed at an early age and may have effects on brain development. Chronic hyperglycemia and microvascular complications are important risk factors common to both type 1 and type 2 diabetes. T2DM is usually diagnosed at an older age and is commonly associated with obesity, insulin resistance, hypertension and dyslipidemia, all of which can have negative impact on brain.

The intimate mechanisms and the risk factors that may lead to the development of more severe cognitive compromise like dementia are object of permanent study.

There is growing evidence that diabetes predisposes to cognitive decline leading to dementia in animal models and humans with both T1DM and T2DM.

Mostly of works demonstrates a link between degenerative dementia in T2DM, and in a lesser degree in T1DM. T2DM is associated with a 50% increase in the risk for dementia and has been associated with compromise of different domains as like attention, processing and motor speed, executive functioning, and verbal memory. Metabolic syndrome and hyperglycemia strongly increase the risk of developing cognitive impairment [19].

Different situations linked to DM increases significantly the risk of cognitive compromise: insulin resistance, altered glucose regulation, utilization of insulin, grade and evolution time of DM, altered glucose tolerance, obesity in midlife and metabolic syndrome are determinants of major cognitive compromise and severity [12].

Clinical stages of cognition dysfunction

The main clinical manifestations in cognitive compromise are considered according the severity of deficits and neuropsychological batteries, beside the clinical evaluation and the information of neuroimaging methods and laboratory results.

Initial and subtle compromise may be described in T1DM and T2DM.

Such compromise appears as a deviation from normal cognitive functioning but is not severe enough to be classified as cognitive impairment.

In T2DM these alterations usually manifest in cognitive batteries, determining values that are one-third to one-half SD lower than in those without diabetes. This compromise is defined by a typical profile that includes altered scores in memory, processing speed and executive function. This changes are subtle and could be observed in late-life onset diabetes [16].

In type T1DM, this compromise of initial changes is more evident, affecting other domains as like general intelligence, psychomotor speed and mental flexibility in one third of patients.

Time of evolution and infantile or young onset diagnosis are factors for major compromise of cognitive spheres in T1DM patients [15].

Mild cognitive impairment (MCI) is a category defined as acquired cognitive complaints with objective abnormal test results in one or more domains on formal cognitive testing. The main difference with dementia is that cognitive deficits should not interfere with daily living activities [17].

According the different domains implicated, MCI could be classified in two categories: memory-impaired (amnestic) MCI and non-memory-impaired MCI. Subjects with MCI have an increased risk of dementia (meta-analysis: RR 3.3), although not everyone with MCI will get dementia [21].

The main importance of MCI as an entity is that could represent the previous step in transit to dementia, and the conversion rate is approximately a 15% annually.

Exploring the relationship between T2DM and MCI, in the diabetic population was observed a 20% increased risk of MCI and also an elevation of the conversion rate from MCI to Dementia [17,20].

Dementia represents the most severe stage of cognitive dysfunction, with objective impairment of multiple cognitive domains, with a marked affection and compromise in daily living activities.

Regarding T1DM, in a study focused on the risk of dementia in a large population (300.000 individuals) concluded that this group of patients had a 65% increased risk to suffer dementia [18].

Instead, in the T2D group, in a population of 1.800.000 individuals, the same study found that T2DM increase the risk to evolve to dementia in a 37% [15].

Comparing the results of other studies and series, and considering the fact that there are more series exploring T2DM than T1DM (mainly due to the number of cases) the presence of DM increases the risk of dementia in a 50% [7,14,18,21,47].

Cognitive profile in T1DM

Different reviews demonstrated that cognitive dysfunctions usually observed in patients with T1DM are associated with the decreased speed of information processing, psychomotor efficiency, attention, memory, learning, problem solving skills, motor speed, vocabulary, visuospatial abilities, visual perception, somatosensory examination, motor strength, mental flexibility and executive function [9].

Selected cognitive domains, including speed of information processing, psychomotor efficiency, visual and sustained attention, mental flexibility, and visual perception, were significantly impaired in patients with type 1 DM compared with those of the controls [23].

The initial series of cases, studying cognitive dysfunctions in T1DM attributed cognitive symptoms to severe and repeated hypoglycemia. This finding is consistent with some reports of severe hypoglycemia that leads to cortical changes in the frontal and temporal lobe, basal ganglia, and hippocampus [13].

Actually, the results of longitudinal epidemiological studies have indicated that chronic hyperglycemia and microvascular complications are more strongly linked to T1DM cognitive compromise, rather than hypoglycemia [15].

Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications is an 18.5-year longitudinal epidemiological study that followed 1,144 participants. Of these participants, 40% had experienced one or more severe hypoglycemic episodes. However, hypoglycemic episodes and cognitive dysfunctions were not significantly associated. In DCCT Study, the factors that were linked with decrease in psychomotor speed over a follow-up period of 18.5 years were: old age, low education, high lifetime hemoglobin A1C (HbA1c) concentrations, proliferative diabetic retinopathy, and renal complications.

Microvascular complications are clearly associated with an increased risk of cognitive decline. An adequate glycemic control plays an important role in the cognitive functions of patients with T1DM. Better glycemic control improves functions, such as psychomotor efficiency, attention, motor speed, memory, and memory.

In the DCCT study, patients with T1DM with a mean glycosylated hemoglobin (HbA1c) of 7.4% had significantly better motor speed and psychomotor efficiency than those with a mean HbA1c of 8.8%. Cognitive function was worse in patients with type 1 DM who presented with DM systemic complications as retinopathy, nephropathy and hypertension. Macro and microvascular complications are clearly associated with an increased risk of cognitive decline [22,23].

Brands., *et al.* performed a meta-analysis to examine the nature and magnitude of cognitive impairment in T1DM. This analysis included 33 studies with participants who were mostly less 50 years of age. The authors reported that compared to non-diabetic controls, people with T1DM had mild to moderate declines (effect size ranging from d −0.3 to −0.7) in multiple domains including intelligence, speed of information processing, psychomotor efficiency, attention, cognitive flexibility, and visual perception In summary, results from both longitudinal and cross-sectional studies show that T1DM is associated with mild to modest decrements in cognitive function. Domains of psychomotor speed, mental flexibility, attention and general intelligence are most commonly affected [9,22,25].

Cognitive profile in T2DM

T2DM is a chronic metabolic disease characterized by hyperglycemia, insulin resistance (IR), and impairment of pancreatic ß-cell function.

There is wide consensus that T2DM and its prodromal state (Insulin Resistance IR) is a pathological condition in which cells fail to respond normally to insulin and have been identified as a risk factor for developing sporadic AD.

Different studies have shown that patients with T2DM are at increased risk of Alzheimer's disease (AD) dementia and vascular dementia [8,11]. Also 17.5% of elderly patients with type 2 DM present with moderate to severe deficits in activities of daily living; 11.3% with cognitive impairment; and 14.2% with depression.

Cognitive dysfunction commonly reported in patients with type 2 DM are associated with recent memory, psychomotor speed, executive function, processing speed, complex motor function, verbal fluency and attention [16].

Adequate glycemic control plays an important role in the cognitive function of patients with T2 DM [48].

In nearly 2,000 postmenopausal women, those with an HbA1c ≥ 7.0% had a four-fold increased risk of developing mild cognitive impairment supporting the hypothesis that worsening glycemic control leads to cognitive dysfunctions similar to those observed in T1DM. The desired value of HbA1c in such study was approximately < 6.0% or > 1.5% lower than that in the standard therapy (targeting level of 7.0 - 7.9%).

The Memory in Diabetes sub study of the Action to Control Cardiovascular Risk in Diabetes trial has reported that aggressive glucose-lowering therapy did not have positive effects on not only cognitive function but also total brain volume during the 40 month follow-up in patients with T2DM [11].

Similar to T1DM, T2 DM is associated with deficits in cognitive function when accompanied by diabetic complications, such as peripheral neuropathy [30].

The duration of type 2 DM and chronic hyperglycemia were associated with changes in cognition. Numerous studies have shown that patients with impaired glucose tolerance had lower scores in memory batteries and altered verbal fluency and worse evolution of dementia compared with healthy subjects [14].

Despite these limitations, data from these prospective studies have shown that people with T2DM perform less well than controls in the cognitive domains of information-processing speed, memory, attention and executive function. Mental flexibility and global cognitive function have also shown to be effected in some, but not in all studies. Decrements in cognitive function in subjects with T2DM have been associated with increased duration of diabetes and poor glycemic control. The ACCORD Memory in Diabetes (MIND) Study was designed to determine if the level of glycemic control impacts cognitive performance over time in nearly 3000 subjects with T2DM. In this study, subjects were either randomized to intensive glycemic control where the target was HbA1c < 6% or to a standard strategy targeting HbA1c to 7% - 7.9%. At baseline, Cukierman-Yafee., *et al.* showed that there was an inverse relationship between cognitive performance and glycemic control as measured by HbA1c [11,35].

Research in animals and humans has shown that type 2 diabetes and its prodromal state, insulin resistance, promotes major pathological hallmarks of Alzheimer's disease (AD), such as the formation of amyloid plaques and neurofibrillary tangles (NFT) [30].

In summary, we can consider two different profiles of cognitive compromise and brain dysfunction according T1DM o T2DM [49].

T1DM has been associated with a decrease in the speed of information processing, psychomotor efficiency, attention, mental flexibility and visual perception, defining a more subcortical profile, with a strong participation of vascular components, white matter involvement and systemic complications. Epidemiological studies of type T1DM showed that chronic hyperglycemia and macrovascular disease, rather than repeated severe hypoglycemia, are associated with the pathogenesis of diabetic related cognitive dysfunction [50].

T2DM has been associated with memory deficits, decreased psychomotor speed, and reduced frontal lobe and executive function, configuring a more cortical subtype of dysfunction. In T2DM chronic hyperglycemia, long duration of DM, presence of associated risk factors as hypertension and obesity, and microvascular complications are associated with the increased risk of developing brain disease and cognition impairment [56].

Pathophysiology of cognitive dysfunction in diabetes mellitus

An enormous and growing amount of bibliography, considering basic science, animal experiences, experimental models, and clinical observations attempt to explain the reasons of the brain and cognition dysfunction in DM. Considering that such compromise is determined by a multifactorial series of variables, we will summarize those that are better known and reviewed.

Glucose metabolism alterations

Regarding energy demand and consumption, brain energy storage is limited, and reduced oxygen or glucose availability impairs brain function. Beside its ability to stored energy, the brain is strongly dependent of the blood glucose levels.

This is probably linked to the availability of enzymes involved in glycolysis, the tricarboxylic acid cycle and ATP biosynthesis.

Consequently, glucose content may be a reflection of neuronal function, and the ratio of glucose utilization can be measured as a parameter to observe changes in brain activity [61].

As a compensatory brain mechanism for excessive glucose utilization, brain glycogen metabolism functions to guarantee brain energy and neurotransmitter metabolism. DM impairs glycogen deposits and synthesis in different brain regions and alters the glucose transportation by increasing the permeability of the blood-brain barrier (BBB) [24].

In diabetic animal models, glycolytic ability and acetyl-CoA activity were reduced which contributed to mitochondrial dysfunction by decreasing ATP production and promoting reactive oxygen species (ROS) and reactive nitrogen species (RNS) formation [62].

Strong interest is related to the role of Apolipoprotein E (APOE), a protein with central participation in lipid metabolism, neurobiology, and neurodegenerative diseases. Neuropathological reports demonstrated that the correlation between DM and AD is particularly strong in individuals carrying the APOE4 allele.

Individuals with the APOE4 allele also have lower glucose metabolism in the posterior cingulate, precuneus, and other brain regions. Related with these findings DM patients with anomalous glucose content and metabolic pathways in the brain have an increased risk of AD [63].

Glucose metabolism is closely related to the pathological development of dementia DM determines glucose transport disorders and metabolic alterations in the body, leading to brain compromise and cognitive dysfunction.

This pathways could act as a possible therapeutic target in order to reduce the incidence of AD in diabetic patients controlling glycemic levels or restoring glucose metabolism. This may also constitute a strategic action in order to anticipate dementia onset or slowing its evolution [40,41].

Energy systems and mitochondrial pathology

Among mitochondria normal function we can consider oxidative respiration, energy metabolism, controlling free radical production and apoptosis, playing an essential role in delaying aging and preventing neurodegenerative diseases [26].

According the high energy demand of the nervous system, the brain is more exposed to mitochondrial failure than other organs. Typical mitochondrial dysfunction implies less ATP production and consequently increasing reactive oxygen species (ROS) generation, determining an oxidative alteration and stress that is translated in oxidative damage of proteins, carbohydrates and lipids [46].

Oxidative stress is a pathological and deleterious condition that appears when cellular metabolic activity is greater than antioxidant capacity or when the amount of free radicals (including ROS and RNS) production and accumulation is difficult to be removed. These facts determines an imbalance between oxidation and antioxidant process that exacerbates oxidative stress, alters mitochondria functions, and leads to mutations in nucleic acids [52].

The amount and accumulation of such pathological residual molecules (ROS and RNS) is increased in diabetic patients that presents cognitive impairment suggesting a physio pathological link between DM and cognitive dysfunction due to insufficient energy supply and reduced antioxidant enzyme activities in the brain [40].

Both neurodegeneration and diabetes are associated with oxidative stress and inflammatory conditions in the CNS that may be mediated partly by mitochondria dysfunction. Dysfunctional mitochondria may be compromised in the production of cellular energy and lose the property of act as an intracellular buffer.

In physiological conditions, aged and damaged mitochondria are turned over and are selectively identified and degraded via an autophagy pathway termed "mitophagy". Another interesting theory about the mitochondrial dysfunction is the altered autophagy mechanism in DM [26,40,53].

Insulin signaling and insulin resistance in the brain

Insulin is the most important anabolic hormone and regulates the metabolism of carbohydrates, lipids, and proteins. Among other basic functions in nervous system modulates the concentration of several neurotransmitters with essential roles in brain activity, such as acetylcholine, norepinephrine, and epinephrine, collaborating with neuronal plasticity and cognitive process [57].

The brain is an insulin-sensitive organ, where insulin signaling regulates energy metabolism, cell survival, and cellular homeostasis, having neuroprotective action. Insulin signaling enhances memory and facilitates synaptic plasticity in the hippocampus, which has an important role in memory and learning [28,29].

In normal conditions, the initial step in the complex insulin signaling pathway is its recognition and binding to a tyrosine kinase receptor, and some of its multiple actions are linked to glycogen synthesis and modulation of phosphorylating kinases, regulating indirectly tau expression and metabolism.

A failure in this complex sequence determines a diminution or absence of insulin effects in the brain leading to tau accumulation that drives to Aβ deposition (and diminished clearance) and also mitochondrial dysfunction. Indeed, such abnormal accumulation and pathway affects the insulin normal signaling, determining an aberrant circuit that could explain neurodegeneration and cognitive impairment [43].

Similar to preclinical works, clinical studies show that disturbed insulin metabolism is a risk factor for cognitive dysfunction, brain atrophy, and dementia. There is evidence that insulin receptor density decreases in aging, and insulin signaling is impaired in AD [59].

Recent works postulates the concept that insulin signaling dysfunction may lead to Aß pathogenesis, which can further impact insulin signaling, closing in this way a vicious and reverberant circuit that leads to neurodegeneration [30].

Insulin-degrading enzyme (IDE), is the main enzyme responsible for insulin degradation, and can also degrade other targets such as glucagon, Aß peptide and also regulates proteasome degradation and other cellular functions [60].

A central concept regarding insulin activity and metabolism is Insulin Resistance (IR) which is defined as a pathological condition in which cells fail to respond normally to insulin. It has been identified as a risk factor for developing sporadic AD.

In the diabetic brain, insulin resistance decreases levels of insulin receptors and reduces insulin signaling that determines impaired synaptic plasticity and memory. Such changes leads to increases GSK-3b activity which increases abnormal tau phosphorylation [19,28].

Different animal models showed that brain insulin resistance may contribute to AD by promoting Aβ generation and hyper phosphorylation of tau protein. Increased brain levels of Aβ correlated with altered insulin signal transduction and autophagy and increased beta-site amyloid precursor protein cleaving enzyme (BACE)1/β-secretase and γ-secretase activities. The results suggest a role of insulin resistance and subsequent hyperinsulinemia in impairing Aβ clearance [36,59].

Classical experimental models injecting Streptozotocin in mice, which results in insulin deficiency, typical of an advanced diabetic stages are related to abnormal brain levels of hyper phosphorylated tau protein. This suggests that insulin resistance may increase the susceptibility for tau pathology especially in the APOEe4 carriers [59]. Other laboratory experiences showed that Insulin can modulate Aβ peptide *in vitro*. The peptide is well known as a neuropathological hallmark of AD. Lower levels of insulin in the brain can decrease the Aβ release into extracellular compartments.

Abnormalities in insulin signaling and insulin receptor (IR) sensitivity in the neuron and dendritic processes in AD have led to the hypothesis that metabolic dysfunction may be related to (IR) [28,29].

Another possible mechanism that could explain why insulin resistance increases the risk of AD is through the clearance and degradation of Aß. Insulin degrading enzyme (IDE) not only breaks down insulin but also degrades Aß. In insulin resistance with high levels of insulin, IDE is saturated by insulin and it is less effective to accomplish with Aß degradation and clearance [60].

In the last years, several studies have shown an association between neurodegenerative disorders as like AD and impaired insulin signaling. Those findings are strongly suggesting that reduced insulin action and insulin resistance may have a central impact in the pathogenesis of neurodegeneration and dementia [28,29].

Different studies have reported that the incidence of clinically diagnosed AD is 1.2 - 1.7-fold greater in patients with T2DM and IR, and several mechanisms were considered: overexpression of inflammatory substances (CRP and IL-6) or dysregulation of HPA axis determining cortisol increasing. Another attractive hypothesis of the importance of IR in cognitive dysfunction involves the role of IR in the ß-amyloid plaques accumulation in AD, considering the fact that IDE participates in the degradation and elimination of ß-amyloid peptide [62].

Due to a reduction of 50% of hippocampal IDE observed in subjects with APOEe4 (compared with other APOE profiles) it was proposed that the ß-amyloid peptide is insufficiently cleared in this group of individuals, followed by its deposition. Through this mechanism IR could determine low amounts of IDE available and a defective ß-amyloid clearance [53].

A major risk to AD is linked to the APOE gene and others genes but the exact genotype/phenotype mechanisms are still incompletely understood. One copy of the APOE e4 allele increases the risk of developing AD by 2-3 fold, but two copies of APOE e4 alleles increase the risk to ~12-fold [46,63].

Expression of ApoE-ε4, which is related to diabetes as well, increases the risk of early onset AD and promotes deposit of Aβ, which is neurotoxic, and also impair its clearance, diminishing protection against oxidative stress and leading to cholinergic dysfunction.

Thus, the combination of IR and APOE-4 allele increases markedly the risk of AD.

Due to another metabolic pathway, insulin resistance affects tau expression and phosphorylation which is normally regulated by insulin. In AD, IR alters signaling through kinases activation as like glycogen synthase kinase-3 beta (GSK-3β). Overactivation of GSK-3β is responsible for tau hyperphosphorylation, followed by tau fibril aggregation and abnormal folding and deposit [40].

In summary, several evidences links Diabetes, IR and AD, trough common mechanisms and shared biochemical pathways (IR determines defective transport and extracellular secretion of Aβ with his subsequent deposition and accumulation, decrease of IDE effect,

altered processing and clearance of amyloid-beta precursor protein peptides (AβPP) and increase of tau phosphorylation and misfolding among other pathological dysfunctions [60].

All this evidences, determines a novel emerging concept that has evolved considering the link between Diabetes and the increased risk of cognitive decline and AD and it is known as Diabetes Mellitus Type 3. The concept of T3DM is recently coined and although is an original proposal must be still validated by the medical community and future steps [27,34,42,50].

Protein metabolism alterations

Diabetes is a general metabolic disease and the protein metabolism is also altered due to the absolute or relative deficiency in insulin availability. In normal conditions anabolic effects of insulin promotes protein synthesis and also protect against protein degrading.

Protein oxidative damage is capable to determine a wide range of age-related diseases, including metabolic disorders such as DM and obesity, cardiovascular complications such as atherosclerosis, and neurodegenerative disorders [31].

Protein accumulation in an aggregated or misfolded structure form is a common finding in neurodegenerative diseases. Different studies showed that the unfolded protein response (UPR) markers such as binding immunoglobulin protein (BIP), phosphorylated protein kinase (PKR) endoplasmic reticulum (ER) kinase (PERK), and others analog substances are involved in neurodegeneration mechanisms [31].

In the same way elevated UPR or ER stress markers are also correlated with tau pathology and neurofibrillary tangles [32].

The common pathological characteristics in DM and AD are the generation of amyloid peptides (APP) and aggregation of abnormal proteins. Growing evidence supports the concept that a series of changes caused by DM can increase the risk for Aß pathology in many AD cases [27].

Recent reports refers to Amylin, a pancreatic hormone secreted with insulin, modulated by food intake and satiety that has a potential role in the neurodegeneration circuit.

Amylin participates in glucose homeostasis and is amylogenic. Its secretion is increased in patients with prediabetes insulin resistance and was observed that hyperinsulinemia coincides with hyperamylinemia. In T2DM patients, were observed deposits of aggregated amylin in the pancreatic islets, kidneys and heart [39].

Other observations confirmed that the brains of patients with T2DM and AD contain an abnormally increased level of aggregated amylin and mixed amylin-Aβ.

These findings could suggest that amylin dyshomeostasis is a possible new link between T2DM and increased risk of AD [12,33,39,51].

Lipid metabolism alterations

Lipids as glycerophospholipids, sphingolipids, and cholesterol are important components of the brain structure but in pathological conditions, as occurs in T2DM an abnormal amount, profile and lipid distribution and metabolism are typical facts observed.

Obesity and dyslipidemia are important risk factors and also central adiposity, elevated triglycerides and low-density lipoprotein cholesterol (LDL-C) and reduced high-density lipoprotein cholesterol (HDL-C) are frequent partners in such pathological process, adding

pathological roads to other metabolic disturbances [40].

Although cholesterol in the nervous system is necessary for several brain functions (synapse and dendritic formation an axonal signaling) hypercholesterolemia could affect the brain blood barrier, increasing its permeability and allowing that peripheral cholesterol enters into the brain, determining metabolic lipid alterations, and promoting Aβ pathology in the brain and further cause oxidative stress, leading to mitochondrial dysfunction and structural damage via lipid peroxidation [24,34].

Cholesterol modulates ß-amyloid peptide levels by affecting secretase function Additionally, the involvement of cholesterol has been implicated in pathogenesis of AD in epidemiological studies.

A possible action target in AD, is given by the fact that when membrane cholesterol levels are decreased, the activities of ß-secretase (BACE1) and secretase are reduced, leading to lower ß-amyloid production [20].

Neuroinflammation and diabetes

Pro-inflammatory substances as like cytokines (IL-6 and TNF) are increased in its expression in the diabetic brain and may participate in neurodegeneration [36].

Experimental models with high fat diet reported augmentation of TNF and anatomical changes in hippocampus microglia that are suggestive of inflammatory activity, associated with altered memory tests in mice [37].

Other evidences suggest that oxidative stress and neuroinflammation are linked processes trough the generation of ROS and activation of advanced glycation end products (AGE/RAGE) and polyol, starting with a pathological cascade that leads to neurodegeneration.

Another pathway to neurodegeneration is mediated by TNF due to its inhibitory effect in insulin signaling, determining more ROS production and accumulation.

Cerebrovascular accumulation of toxic lipids, advanced glycation end products (AGEs) and aggregated proteins trigger inflammatory responses and secretion of inflammatory mediators in the circulation.

Inflammatory responses are associated with blood-brain barrier (BBB) breakdown BBB injury further exposes brain parenchyma to neurotoxic blood proteins, thrombin, fibrin, plasmin, hemoglobin, and iron from lysed red blood cells. A leaky BBB causes abnormal neuronal activity that plays a role in diabetes-associated neurological deficits [24,44,45].

Conclusion and Perspectives

Diabetes and its complications has dramatically increased its prevalence and diffusion in the last 20 years due to multifactorial issues. Both T1DM and T2DM are associated with variable compromise in cognitive function, with a wide spectrum of impairment, ranging from subtle deficits in cognition to severe dementia.

Increased awareness about the risk of cognitive impairment in diabetes among medical community is needed in order to promote active screening, especially in the population at-risk.

Patients and their families should be counseled about risk factors associated with cognitive decline. Screening for cognition dysfunction should be considered in the total exposed population and mandatory in subjects with cognitive complaints.

More research is needed to develop specific diagnostic criteria, scores and strategies to identify people who are at increased risk of developing accelerated or clinically significant cognitive decline, implementing emerging guidelines.

Course-modifying treatment and prevention strategies for diabetes-associated cognitive dysfunction, especially in those risk factors in which adequate interventions could modify the prognosis and quality of life of our patients, is one of our challenges.

One of the important reasons for the active research in these fields is the promising fact that antidiabetic drugs may play a preventive or therapeutic role in cognitive dysfunction.

Neurodegeneration and cognitive impairment in may be prevented or avoided with the early treatment of antidiabetic agents, such as PPAR agonists, Intranasal Insulin, GLP-1, Glitazones or other pharmacological interventions.

Longitudinal and prospective studies with long- term follow up are needed to understand and clarify the underlying factors that leads to the development of diabetes related cognitive dysfunction [54,55,57,58].

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