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Review

Cognitive and motor perturbations in elderly with longstanding diabetes mellitus

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ABSTRACT

Type 2 diabetes mellitus is a chronic disease characterized by insulin resistance; inflammation; oxidative stress; vascular damage; and dysfunction of glucose, protein, and lipid metabolisms. However, comparatively less attention has been paid to neurologic alterations seen in elderly individuals with type 2 diabetes. We review clinical, metabolic, and biochemical aspects of diabetic encephalopathy (DE) and propose that quality of dietary lipids is closely linked to DE. This implies that preventive nutritional interventions may be designed to improve DE.

Introduction

Diabetes mellitus (DM) is a complex, chronic, systemic, metabolic disorder that can have deleterious effects on several target organs and systems such as the heart, eye, kidneys, vascular tissues, nervous system, and the brain. It is the leading cause of end-stage renal disease, loss of vision, neuropathy, and cardiovascular disease (CVD) [1,2]. Additionally, an increasing number of elderly individuals with DM exhibit cognitive impairment and motor dysfunctions that can cause postural balance impairment—features that together are known as *diabetic encephalopathy* (DE) [2–4]. The physiopathology of DE could be attributed to long-standing hyperglycemia, elevated blood pressure, hyperinsulinemia, frequent and severe episodes of hypoglycemia, and dyslipidemia. These cardinal metabolic alterations are enhanced through phosphorylation of tau protein, favoring the formation of neurofibrillary tangles [5–7] and diminished amyloid breakdown caused by insulin degrading enzyme deficiency [8–10] that, in turn, can result in the development of Alzheimer's disease (AD) [11]. Abnormal accumulation of advanced glycated-end products (AGEs) in the brain, chronic and persistent systemic low-grade chronic inflammation (LGCI) [12], increased apoptosis resulting in neuronal loss [9,10,13,14] may result in accelerated brain aging [15,16].

The objective of this review is to discuss and summarize the pathophysiology of DE and to suggest how supplementation of polyunsaturated fatty acids (PUFAs) may prevent DE. This review was designed based on data collected from existing literature (obtained from PubMed), clinical experience, research results, and critical review of the literature based on its relevance, update, and quality of journals.

Multiples roles for insulin in the brain

The presence and expression of insulin receptors (IRs) in the hippocampus and cerebral cortex emphasize their major role in the cognitive process [17–19]. The expression of glucose

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transporter type (GLUT) 4 and GLUT8 receptors in the brain emphasize not only the role of GLUTs but also that of insulin in central nervous system (CNS). There appears to be a close association among pancreatic islets signals, the gastrointestinal tract, and the brain in the control of energy homeostasis [20,21]. Similar to leptin, insulin interacts with paraventricular nuclei of hypothalamus to modulate food intake, glucose homeostasis, adipogenesis, and obesity. Additionally, insulin may facilitate learning and improve memory; however, in conditions of insulin deficiency and insulin dysfunction or resistance, it may lead to cognitive impairment and also development of obesity [22].

Dietary practices in humans are based on cultural factors such as availability of food that may affect meal composition and calorie intake and density. Previous studies showed that dietary practices labeled as "Western pattern" may enhance the risk for development of obesity, DM, chronic inflammation, lithiasis, and certain types of cancer (colon, urinary tract, endometrial, and breast) [23–28]. Following the intake of food, the gut is stimulated by ingested nutrients releasing several peptides depending on the quantity and quality of the calories consumed. Once hypothalamic neurons sense the amount and quality of food taken, a feeling of satiety may occur that results in halting further food intake. Duodenal peptide cholecystokinin appears to be one such satiety signal originating from the gut [20].

Loss of body weight is associated with a decrease in the secretion of insulin and leptin, which activate satiety/hunger regulatory centers in the hypothalamus [20]. Both molecules interact with neurons in the arcuate nucleus and participate in melanocortin synthesis that controls energy expenditure [16]. IR participates in the peripheral and central glucose metabolism regulation [18]. Activated IR has kinase activity on two major pathways, phosphoinositide-3 kinase [PI3 K]/Akt and Ras-mitogen-activated protein kinase [29,30] (Fig. 1). This metabolic cascade regulates protein synthesis; glucose, lipid, protein, and mineral metabolism; cell growth; and differentiation [29–31]. In the hippocampus, these molecular signals are linked to memory [32]. These pathways also modulate PI3 K/Akt/mTOR to increase the sensitivity of glutamate *N*-methyl-d-aspartate receptor, which is involved in the excitatory state of neurons [32–35].

Pathobiology of DE

Streptozotocin (STZ)-induced DM rats showed neuronal and glial degenerative abnormalities including perivascular edema and mitochondrial swelling, myelin sheath disarrangement, increased demyelinated axons areas, presynaptic vesicle dispersion in swollen axonal buttons, neurofilament fragmentation, and oligodendrocyte alterations in the cortex hypothalamus and cerebellum [15,36].

Microstructural alterations in white matter of younger obese individuals may precede brain atrophy, cognitive impairment,

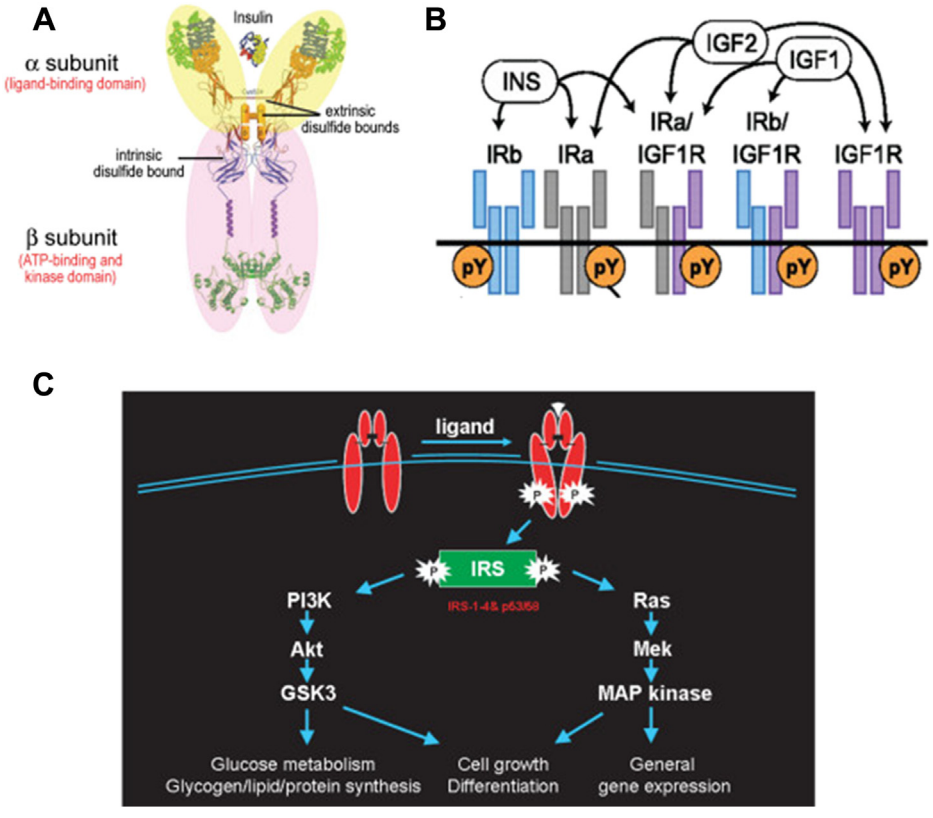

Fig. 1. Insulin receptor structure and signaling. (A) Insulin receptor monomer, composed of an α (yellow) and β subunit (pink) bridged by an intrinsic disulfide bond, which dimerizes with another insulin receptor monomer through extrinsic disulfide bonds to form a functional receptor. (B) Ligand selectivity of the insulin receptor homodimer or heterodimer with the insulin-like growth factor (IGF)-1 receptor. Note that the homodimer of the splice variant IRa, the predominant form of insulin receptor in the brain, binds specifically to insulin (INS), whereas the heterodimer with the IGF-1 receptor binds to not only INS but also IGF-1 and IGF-2. (C) Insulin receptor signaling initiated by ligand binding activates tyrosine autophosphorylation in the β subunit, which stimulates two major downstream pathways, the phosphoinositide-3 kinase (PI3 K)/Akt and Ras/mitogen-activated protein kinase (MAPK) cascades, through insulin receptor substrates (IRSs) and results in a diverse series of cellular processes in peripheral tissues. Adapted and modified from Shu-Ling Chiu and Hollis T: Cline Insulin receptor signaling in the development of neuronal structure and function. Neural Dev. 2010;5:7. The color version of this figure is available online at www.nutritionjrnl.com.

or both in those with metabolic syndrome (MetS) [37]. Brain autopsy studies reported microscopic vascular and nonvascular white matter abnormalities in patients with type 2 diabetes mellitus (T2 DM), which are not detected with conventional structural magnetic resonance imaging but recorded with diffusion tensor imaging, a non-invasive technique that is sensitive to white matter fiber damage, demyelination, and axonal changes [38,39].

Perturbation of IRs plays an important role in the pathogenesis of insulin resistance (IRe), obesity and MetS. Mice with IR gene disruption specifically in the neurons (neuron-specific insulin receptor knockout), mainly females, showed increased food intake. Both male and female mice developed diet-sensitive obesity, increased plasma leptin levels, mild IRe, hyperinsulinemia, and hypertriacylglycerolmia [40], features that are reminiscent of T2 DM and MetS in humans. These results emphasize the importance of neuronal IRs in glucose homeostasis and their role in the pathogenesis of obesity, T2 DM, and MetS. Stilmann-Salgado rats [e-SS], a non-obese model of DM, developed mild T2 DM at 6 mo of age with liver and renal impairment, similar to diabetic nephropathy [41,42], in which we noted a significant neuronal apoptosis that could be related to the development of DE (unpublished data).

Molecular basis linked to neuronal death in DE

Under hyperglycemic conditions, extracellular proteins and hemoglobin are progressively glycated (nonenzymatic glycosylation) resulting in the formation of AGEs that stimulate the receptor of AGEs (RAGE) and integrins linked to cell membranes that lead to the overexpression of 3-inositol and overstimulation of MAPkinase and ERKinase pathways. These changes result in paraptosis, a non-apoptotic cell death program. Paraptosis is induced by insulin-like growth factor I receptor (among other inducers) and is mediated by mitogen-activated protein kinase [43], which may lead to programmed cell death in the CNS [44] that could underlie the development of DE.

Hypoglycemia

Hypoglycemia is linked to cognitive dysfunction and, in turn, cognitive impairment [45]. Repetitive episodes of moderate to severe hypoglycemia have been implicated in the development and progression of cognitive dysfunction seen in DE. During acute hypoglycemic episodes, the performance of immediate verbal and visual memory, working memory, delayed memory, visuomotor and visuospatial skills, and global cognitive dysfunction are impaired. These abnormalities occur despite glucose levels being brought to near normal by the triggering of counterregulatory hormones in many individuals [46]. In young patients with DM, enlargement of the hippocampus was observed, reflecting pathologic reaction to hypoglycemia, which may disrupt normal development of brain and results in gliosis and reactive neurogenesis [47]. Indeed, a close association between multiple severe episodes of hypoglycemia and impaired cognitive function in patients with T1 DM was reported in the Diabetes Control and Complications Trial (DCCT) [48]. Results from the DCCT found cognitive perturbations to be significant because elderly brains are more sensitive to hypoglycemia [48–50].

Hyperglycemia

Hyperglycemia may contribute to DE as a result of the activation of the sorbitol–aldose reductase pathway, which reduces excess glucose to sorbitol, and increases the formation of AGEs, which also has been implicated in microvascular damage to retina, kidneys, and nerves. Diabetic mice with cognitive impairment showed increased expression of AGEs, enhanced generation of reactive oxygen species, and activation of protein kinase C in neurons and glial cells, together with alterations in white matter and myelin [3,51–53]. STZ-induced diabetic rats showed increased sorbitol levels in cranial and sciatic nerves, cerebral cortex, and retina [15]. Sorbitol accumulation was reduced significantly when the animals were treated with the aldose reductase inhibitors tolerstat and sorbinil, which corresponded with improvement in cognitive function [53,54]. Altered neurotransmitter function, cognitive dysfunction, and impairment of long-term potentiation reverted to normal after treatment with insulin in this murine model [55].

Glycemic variability

In both types 1 and 2 diabetes, a strong association has been shown between development of the disease and average mean levels of glycemia measured as hemoglobin A_{1c} (HbA_{1c}), and the occurrence of target organ damage. Altered values of HbA_{1c} could be closely related to microvascular complications seen in the retina, renal tissue, and peripheral nerves, and accelerated atherosclerotic macrovascular disease affecting the heart, the brain, and the lower extremities [56]. These results emphasize the importance of good glycemic control to prevent target organ damage in DM.

Role of vascular disease

Longstanding DM is known to increase the risk for thrombotic strokes and vascular diseases by almost two- to sixfold [45]. Microvascular complications, atherosclerosis, and severe hypoglycemic events increase the risk for dementia [57]. Autopsy studies revealed that patients with longstanding type 1 and 2 diabetes showed histopathologic abnormalities related to vascular diseases such as diffuse brain degeneration, pseudocalcinosis, and cranial nerve demyelization along with capillary basement membranes thickening [58,59].

Insulin resistance

The brain is an insulin-dependent organ [60,61]. IRs and their mRNA expression are widely seen in rat brain, especially in the olfactory bulb, hypothalamus, hippocampus, cerebellum, piriform cortex, cerebral cortex, and amygdale [61]. In humans, positron emission tomography (PET) revealed an increase in brain glucose metabolism in the setting of hyperinsulinemia and decrease in individuals with peripheral IRe [62]. Patients with memory impairment and AD exhibited improvement in verbal memory following intranasal instillation of insulin, which had no effect on peripheral glucose or insulin levels but increased CNS insulin levels [63]. Patients with AD have reduced cerebral glucose uptake as measured by PET and also showed less GLUT8 in brain capillaries, frontal cortex, hippocampus, caudate nucleus, parietal, occipital, and temporal lobe compared with healthy controls [64,65]. IRe contributes to cognitive dysfunction when associated with formation of senile plaques [66–68]. Thus, some of the factors that could contribute to brain damage seen in diabetics include cerebral vascular atherosclerosis, hypertension, hyperglycemia, obesity, dyslipidemia, and IRe [64,69].

Cortisol

Patients with T2 DM have an up-regulation of the hypothalamic–pituitary–adrenal axis, with increased serum cortisol compared with controls [70,71]. Patients without diabetes treated with dexamethasone, corticosterone, and hydrocortisone performed worse in memory testing [72]. Patients with Cushing's disease have decreased memory performance, attention, reasoning, and concept formation compared with healthy controls. The abnormalities in Cushing's could be attributed to a significant reduction in cerebral glucose metabolism as recorded by PET scan. In animal studies, treatment with glucocorticoids induced structural and consequent functional changes in the hippocampus neurons [73,74].

Inflammation

The exact reason for the association of LGCI with diseases such as obesity, CVDs, T2 DM, and cancer is not well understood. Inflammation is a protective response that unavoidably occurs at the cost of normal tissue function. Substantial changes in environment that results in epigenetic changes in the expression of several genes, which are inherited by the progeny, maladaptation to the changes in the environment, and changing food habits could outpace genetic adaptation through natural selection and may lead to increase in disease susceptibility [75]. T2 DM is an LGCI process with higher levels of inflammatory markers such as C-reactive protein, α1-antichymotrypsin, interleukin-6, and intercellular adhesion molecule 1 compared with control populations [76,77]. Increased activation of the renin–angiotensin system has been related to CVD. The detrimental effects of T2 DM on the renin–angiotensin system with regard to insulin secretion are mediated by a reduction in pancreatic blood flow and induction of islet fibrosis and oxidative stress, as well as persistency of LGCI [78,79].

LGCI is associated with a hyperlipidemic state, preceding the diagnosis of diabetes, which up-regulates the production of proinflammatory cytokines and toll-like receptors [80]. Diabetic neuropathy, the most frequent chronic diabetic complication, is related to oxidative stress and systemic LGCI [80].

Inflammation and microglia activation also are related to neurodegenerative diseases [81,82]. Low-grade systemic inflammation is also noted in erectile dysfunction (ED), diabetic polyneuritis, and in patients with chronic neurodegenerative processes, suggesting that diabetic encephalopathy could be considered a neurodegenerative disease.

Lipid metabolism

DM is associated with impaired metabolism of essential fatty acids (EFAs) as a result of decreased activity of Δ6 and Δ5 desaturases, enzymes that are essential for the conversion of the dietary EFAs linoleic and α-linolenic acids, to their respective long-chain metabolites, including γ-linolenic acid, arachidonic acid, and eicosapentaenoic acid, and docosahexaenoic acid (DHA), respectively. This may explain reduced arachidonic acid and DHA levels in the membrane phospholipid of neurons and sciatic nerves in patients with DM [83].

Additionally, excess consumption of calories, impaired glucose tolerance, abdominal or central obesity, hypertension, hypertriacylglycerolmia, and reduced high-density lipoprotein cholesterol all seem to play an important role in the development of age-related cognitive decline, mild cognitive impairment, vascular dementia, and AD [84].

Palmitic acid (PA), one of the most common saturated fatty acids found in Western food such as butter, cheese, milk, meat, and seed oils, activate macrophages [85]. PA also increases proinflammatory cytokine and chemokine expression in myotubes, phosphorylated c-Jun-NH2-terminal kinase, and other markers of inflammation and at the same time suppress α-β-κ protein expression and phosphorylated AKT [85]. High levels of saturated and monounsaturated fatty acids, such as PA and oleic acid, when combined with hyperinsulinemia, may activate human monocytes to produce proinflammatory cytokines such as interleukin-6, which contributes to the development of LGCI, that is characteristic of IRe [86]. Neuroinflammation is believed to be one of the downstream events in the pathologic cascade of AD and ED. Imbalance in the form of excess consumption of saturated fatty acids and trans-fats may induce EFA deficiency [87]. PA reduces the activity and expression of insulin-degrading enzyme (IDE), a key protease responsible for the degradation of amyloid beta (Aβ) in neurons [88]. Prolonged exposure to free fatty acids, PA, and oleic acid, reduced glucose-stimulated insulin secretion, and increased apoptosis of human pancreatic β-cells that seems to be partially dependent on ceramide and by down-regulation of Bcl-2 [89,90]. In contrast to this, incubation with DHA up-regulated IDE levels in primary hippocampal neurons, showing differential effects of saturated fatty acids and PUFAs on IDE expression [88].

Insulin-degrading enzyme

Neprilysin and IDE play a key role in degrading amyloid monomer, a building stone of the plaques Aβ of AD, so up-regulation of IDE may be a useful approach to reduce amyloid deposit [91]. IDE activity is significantly decreased in individuals with mild cognitive impairment, and plays an essential role in insulin homeostasis, implicating a close relationship between AD and T2 DM [92]. Treatment of hippocampal neurons with insulin increased IDE protein levels by 25%, and led to PI3 K activation that is evidenced by Akt phosphorylation, which was blocked by PI3 K inhibitors [91,93].

Amyloid

Pancreatic islets in patients with T2 DM are characterized by β-cell loss and deposition of islet amyloid, findings that mimic neuronal loss and Aβ deposition seen in AD [94,95]. The composition of islet and neural β-amyloid are similar and are toxic to cells. Decreased function of Aβ-protein and IDE may underlie or contribute to AD. This may explain the recently recognized association among hyperinsulinemia, diabetes, and AD [95] .

Oxidative stress

Hyperglycemia is linked to impaired mitochondrial function, which might play an important role in accelerated oxidative damage observed in the brain of individuals with diabetes. T2 DM is associated with increased oxidative stress, which may lead to an increase in DNA damage that could be ameliorated by a healthy diet that contains well-balanced antioxidants [96]. There is a close relationship between oxidative stress and AMPK activation in various chronic disorders, including chronic degenerative brain disease seen in diabetes [97–99]. In the STZ-induced model of DE, brains displayed up-regulated protein expression of AdipoR1, p-AMPKα1, Tak1, GLUT4, NADPH oxidase subunits, caspase-12, and 3-NT and increased lipid peroxidation compared with controls [98,99].

Impaired tau phosphorylation

T2 DM is reported to increase the risk for dementia, including AD. A decrease in the levels and activities of several components of the insulin–PI3 K–AKT signaling pathway was found in AD and T2 DM [92]. The deficiency of insulin–PI3 K–AKT signaling was more severe in individuals with both T2 DM and AD. This could lead to the activation of glycogen synthase kinase-3 β and major tau kinase. Levels and activation of the insulin–PI3 K–AKT signaling components are correlated negatively with the level of tau phosphorylation and positively with protein *O*-GlcNAcylation, suggesting that impaired insulin–PI3 K–AKT signaling might contribute to neurodegeneration [92]. In STZ diabetic rats, hippocampus tau protein also was hyperphosphorylated, accompanied by lowered phosphorylation levels of Akt, GSK-3, and protein phosphatase-2 A [99].

Clinical features of DE

Advances in the management of acute hyperglycemia have virtually eliminated frequent complications of diabetes seen in the past such as premature death due to hyperosmolar or acetoacidotic coma. Indeed, a better understanding of the molecular basis of glycosylation, atherosclerosis, and ischemia in both microvascular and macrovascular beds resulted in a reduction of vascular complications when applied properly in a timely manner along with appropriate advice regarding nutrition and healthy lifestyle. These combined strategies led to increased life expectancy of patients with T2 DM thus reaching ages similar to the general population. As a result, this increased life expectancy led to the recognition of a relatively new complication described in 1992 as DE [3–5]. Patients with longstanding diabetes (both types 1 and 2) have cognitive perturbations [100,101]. The age of onset of diabetes and poor control of hyperglycemia are contributing factors to cognitive dysfunction seen in this population [100,101]. Motor and cognitive dysfunctions are evident when patients with diabetes show slowing information-processing speed; worsening psychomotor efficiency; and perturbations in motor speed, vocabulary, general intelligence, visuoconstruction, attention, somatosensory examination, motor strength, memory, and executive functions [45]. These abnormalities are significantly more precocious and severe in patients with diabetes compared with non-diabetics, leading to significant and progressive deterioration in higher mental capacities [102]. Progression of DE is evidenced by heavy perturbation of attention, recent declarative, procedural, spatiotemporal, and delayed memory. The ability to plan, learn new concepts and skills, development of verbal or written speech, and associate ideas with fluidity increasingly deteriorate. Not only are intellectual abilities affected, motors skills are also damaged as these individuals may no longer be able to walk quickly, and may become hesitant in balance, thus leading to falls. Sleeping disturbances, insomnia, and early awakening often are recorded. These patients frequently develop depression, which correlates with the discussed perturbations in PUFA metabolism in major mood disorders such as depression and bipolar disorder [103]. The slow evolution of ED allows the patient, family, and close relatives to adapt to these changes and hence, they may go unnoticed [101]. Eventually, progression of ED could interfere with daily routine tasks such as misapplication of insulin, taking medicine, and eating, and may even result in the occurrence of dangerous accidents in the home. Psychological diagnostic testing may corroborate these symptoms. Patients with a score <23 on the Mini-Mental Status Exam fared worse on measures of self-care and ability to perform activities of daily living, and the clock, set, and Yesavage tests [104]. Cerebral atrophy was confirmed in these patients with ED by magnetic resonance imaging studies [105–107] (Fig. 2).

Nutrition therapeuthic options and approaches

Antioxidants

A proanthocyanidin, naturally occurring antioxidant derived from grape seed extract seems to reduce injuries to diabetic rat cerebral cortex by modulating RAGE/nuclear factor-κβ p65 pathway [98,108]. Curcumin could prevent hyperglycemia-mediated DE, by down-regulation of AMPK-mediated gluconeogenesis in addition to its antioxidant property [99,109]. However, excess of antioxidants also may be harmful because oxidation is a complex cellular phenomenon vital for normal metabolism. Hence, maintaining appropriate balance between pro- and antioxidant molecules is important to prevent several diseases [110–112].

Docosahexaenoic acid

As already discussed, cognitive impairment is related to neuroinflammation. It is known that ω-3 PUFAs have anti-

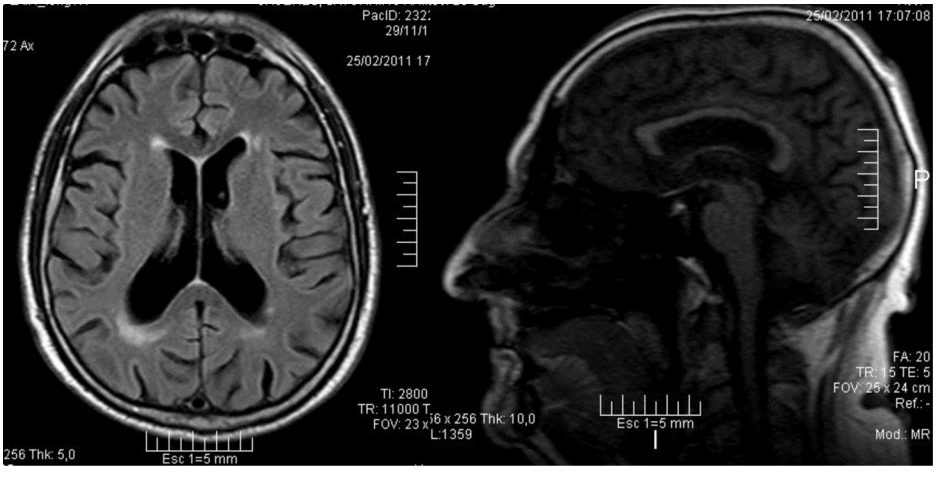

Fig. 2. Cerebral resonance nuclear magnetic image of a 70-y-old man with type 2 diabetes mellitus, with insulin-requirement for 10 y, hypertrygliceridemic, with heavy cognitive impairment. Image shows enlarged ventricles and cortical and temporal atrophy.

inflammatory action [111–114]. In a diabetic rodent model, DHA supplementation decreases reactive oxygen species and inflammatory cytokine production in microglial and neuronal cells, attenuating degenerative changes in hippocampus [113,115]. DHA also attenuated Aβ secretion, enhanced neuroprotectin synthesis, which represses inflammation, oxidative stress, and cell apoptosis induced by Aβ 42, and thus promoted neuronal survival [115]. Fish oil dietary supplementation, a rich source of ω-3, exerts neuron-protective function in diabetic rats through antiapoptotic pathways and significantly improved the ability of learning and memory [116–118].

Conclusion

The pathophysiological mechanisms involved in the onset and progression of DE include longstanding DM, alterations in glucose and lipid metabolism, oxidative stress, increased levels of AGEs, IRe, low efficiency of IDE enzyme, and persistent LGCI. Changes in these bioactive molecules could result in decreases in neuronal survival, neurofibrillar accumulation, and widespread cell death via paraptosis, which ultimately result in the onset and progression of DE.

As discussed here, ED may be prevented or delayed, at least partly, by regular consumption of dietary nutraceuticals like ω-3 PUFAs and natural antioxidants in optimal amounts. Some of the approaches that could be of therapeutic benefit in ED include regular consumption of ω-3 PUFAs and natural antioxidants, healthy lifestyle, and strict control of hyperglycemia.

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