Biochimica et Biophysica Acta 1792 (2009) 432–443

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbadis

Review

(Pre)diabetes, brain aging, and cognition

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ARTICLE INFO

Article history:
Received 3 November 2008
Received in revised form 8 December 2008
Accepted 8 December 2008
Available online 16 December 2008

Keywords:
Diabetes
Insulin
'Brain aging'
Cognition
Dementia

ABSTRACT

Cognitive dysfunction and dementia have recently been proven to be common (and underrecognized) complications of diabetes mellitus (DM). In fact, several studies have evidenced that phenotypes associated with obesity and/or alterations on insulin homeostasis are at increased risk for developing cognitive decline and dementia, including not only vascular dementia, but also Alzheimer's disease (AD). These phenotypes include prediabetes, diabetes, and the metabolic syndrome. Both types 1 and 2 diabetes are also important risk factors for decreased performance in several neuropsychological functions. Chronic hyperglycemia and hyperinsulinemia primarily stimulates the formation of Advanced Glucose Endproducts (AGEs), which leads to an overproduction of Reactive Oxygen Species (ROS). Protein glycation and increased oxidative stress are the two main mechanisms involved in biological aging, both being also probably related to the etiopathogeny of AD. AD patients were found to have lower than normal cerebrospinal fluid levels of insulin. Besides its traditional glucoregulatory importance, insulin has significant neurothrophic properties in the brain. How can clinical hyperinsulinism be a risk factor for AD whereas lab experiments evidence insulin to be an important neurothrophic factor? These two apparent paradoxal findings may be reconciliated by evoking the concept of insulin resistance. Whereas insulin is clearly neurothrophic at moderate concentrations, too much insulin in the brain may be associated with reduced amyloid-β (Aβ) clearance due to competition for their common and main depurative mechanism — the Insulin-Degrading Enzyme (IDE). Since IDE is much more selective for insulin than for Aβ, brain hyperinsulinism may deprive Aβ of its main clearance mechanism. Hyperglycemia and hyperinsulinemia seems to accelerate brain aging also by inducing tau hyperphosphorylation and amyloid oligomerization, as well as by leading to widespread brain microangiopathy. In fact, diabetes subjects are more prone to develop extense and earlier-than-usual leukoaraiosis (White Matter High-Intensity Lesions — WMHL). WMHL are usually present at different degrees in brain scans of elderly people. People with more advanced WMHL are at increased risk for executive dysfunction, cognitive impairment and dementia. Clinical phenotypes associated with insulin resistance possibly represent true clinical models for brain and systemic aging.

1. Introduction

Diabetes mellitus (DM) is one of the most important and prevalent chronic diseases. It currently affects 250 million people worldwide, with 6 million new cases reported each year [1]. This prevalence rises with age from 12% in people aged 65 to 70 to 15% in people over age 80 [2]. DM is a systemic disease that can damage any organ in the body [3]. Complications include pathologic changes involving both small and large vessels, cranial and peripheral nerves, skin, and eyes. These organic lesions may lead to hypertension, renal failure, vision loss, autonomic and peripheral neuropathy, peripheral vascular disease, myocardial infarction and cerebrovascular disease, including stroke [3].

In recent years, significantly more interest has been dedicated to the effect of diabetes on the brain. Along with cerebrovascular disease, diabetes is implicated in the development of other neurological comorbidities. Less addressed and not as well recognized complications of DM are cognitive dysfunction and dementia. Like *diabetes*, cognitive dysfunction represents another serious problem and is rising in prevalence worldwide, especially among the elderly [4]. Diabetes mellitus has been implicated as risk factor for dementia not only of vascular type but also to Alzheimer's disease (AD) [5] Patients with type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) have been found to present cognitive deficits, associated with reduced

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doi:10.1016/j.bbadis.2008.12.003

Table 1
Summary of cognitive functions found to be affected in Type 1 (T1DM) and Type 2 diabetes mellitus (T2DM)

Cognitive functions	T1DM	T2DM
Verbal memory	↓	↓*
Nonverbal memory	↓	↓*
Attention	↓*	↓
Visuospatial performance	↓*	–
Processing speed	↓*	↓*
Executive function	↓*	↓*
Psychomotor efficiency	↓*	–
General intelligence	↓	–

↓: decreased; – does not seem to be affected or evidence lacking. Note: domains marked by asterisks have particularly strong supporting data (see Refs. [23] and [62]).

performance on multiple domains of cognitive function. Cognitive impairment due to *diabetes* mainly occur at two main periods: during the first 5–7 years of life when brain systems is in development; and the period when the brain undergoes neurodegenerative changes due to aging (older than 65 years) [6].

Anatomic brain alterations have been identified in patients with both T1DM and T2DM [7–13]. These include generalized brain atrophy and greater high-intensity lesion volumes, predominantly in the subcortical regions [13]. Patients with diabetes mellitus are more likely to present earlier and more extense leukoaraiosis (White Matter Hyperintense Lesions (WMHLs) [14]. Leukoaraiosis is a feature usually found in brain scans performed in subjects over 80 years-old [15]. The nature of these WMHLs is uncertain, but investigators have hypothesized that they could represent demyelination, increased water content or gliosis [16]. Magnetic Resonance Imaging (MRI) has also demonstrated that subjects with T2DM have hippocampal and amygdala atrophy relative to control subjects [17]. The hippocampus and amygdala are responsible for such functions as memory and behavior and, coincidentally, are also found to be atrophied in AD [17]. In addition, post-mortem studies of brains of DM patients with dementia often reveal the coexistence of both brain microvascular lesions and extense amyloid plaque burden, a characteristic of AD. This phenomenon suggests that diabetes is a risk factor for both vascular dementia (VD) and AD [18].

Many studies suggest that the risk of cognitive decline and neurodegeneration is increased not only in DM, but also in patients with pre-diabetes and metabolic syndrome (MetS) [19]. Individuals with pre-diabetes are defined as those presenting impaired fasting glucose and/or impaired glucose tolerance [20], what increase their risk of developing frank DM. Those subjects already present insulin resistance (IR) as a pathophysiological mechanism that is often associated with MetS [19,20]. Metabolic syndrome, in turn, is a cluster of interrelated cardiometabolic risk factors including visceral obesity, dyslipidemia (elevated triglycerides and/or low HDL-cholesterol), hypertension, dysglycemia (pre-diabetes or diabetes) [21] Subjects with the MetS often also present a proinflammatory/prothrombotic state. MetS has already been associated with silent strokes, cognitive impairment, vascular dementia, Alzheimer's disease and the 'frontal-subcortical (geriatric) syndrome' (FSCS) [see [22] for a review].

The exact pathophysiology of cognitive dysfunction and cerebral lesions in diabetes mellitus is not completely understood, but it is likely that hyperglycemia, vascular disease, hypoglycemia, and insulin resistance play significant roles [23]. Diabetes mellitus may accelerate the brain aging process, as it accelerates cerebral atrophy [24], thus reducing cognitive reserve and the threshold for the development of AD symptoms. In addition, DM may interfere with cerebral amyloid and tau metabolism [25]. Alterations in insulin and glucose homoeostasis in the periphery may affect brain insulin and its receptor functions [25], promoting increasing oligomerization of β-amyloid, and inducing tau hyperphosphorylation [25,26]. Insulin resistance seems also to accelerate biological aging by fostering the formation of Advanced Glycation End-products (AGE) and, consequently, ROS (Reactive Oxygen Species) [27]. The relation between insulin and the metabolism of amyloid-β peptide (Aβ) and tau in particular has been receiving increasing attention over the past few years [25,26].

2. Global and specific subtypes of cognitive dysfunction in:

2.1. Type 1 diabetes

Neuropsychological studies have shown that patients with T1DM perform worse than patients without T1DM on several cognitive functions. Although the degree of magnitude is variable, this worse performance in cognitive functions is already noticeable during childhood [28]. These cognitive functions include specific deficits of intelligence, attention, processing speed, memory, and executive skills [29–38]. Cognitive deficits were mainly identified in information processing speed [29,30] and psychomotor abilities. The progression and accumulation of these specific deficits can lead to global deficits and dementia in diabetic patients [31,32]. The cognitive performance of diabetic patients is summarized in Table 1 and the neurocognitive tests utilized on these studies are shown on Table 2.

In addition, other deficits were also identified such as those involving motor speed [33,34,35] and strength [35], vocabulary [36,37], general intelligence [36,39], visuoconstructional praxis [36], attention [39], memory [32], and executive function [32,38]. A recent meta-analysis analyzed 33 studies of cognitive function in adults with T1DM and found significant reductions in overall cognition, both fluid and crystallized intelligence, speed of information processing, psychomotor efficiency, visual and sustained attention, mental flexibility, and visual perception, when compared with controls [40]. There was no significant difference in motor speed, memory, selective attention, and language. Lowered cognitive performance in diabetic patients appeared to be associated with the presence of microvascular complications, but not with the occurrence of severe hypoglycemic episodes or with poor metabolic control [40].

Many longitudinal studies have found lower intelligence quotient (IQ) scores, reduced mental efficiency, and worse school performance in children with T1DM [37, 38, 41,42]. Nevertheless there are many factors that can influence on the cognitive performance of these

Table 2
Main types of cognitive tests utilized in the specific assessment of the diverse cognitive subfunctions cited in Table 1

Cognitive functions	Assessment
Verbal memory	Paragraph recall/Contextual tasks (immediate; delayed); Word List Recall/Noncontextual tasks; (immediate; delayed); Verbal recognition.
Nonverbal memory	Figural reproductions (immediate; delayed).
Attention	Arithmetic performance (e.g., serial subtraction tasks); Digit Span subtest of the WAIS-R (Wechsler, 1981) and WAIS-III (Wechsler, 1997); Block Span (E. Kaplan et al., 1991).
Visuospatial performance	Measures requiring construction and organization of objects or designs.
Processing speed	Reaction time measures; Digit Symbol Coding subtest of the WAIS-R; Trails A (Spreen and Strauss, 1991); Stroop tasks (color or word naming) (Spreen and Strauss, 1991).
Executive function	Letter and category fluency measures; Abstract conceptualization measures; Measures of verbal and nonverbal reasoning abilities; Working memory tasks; Wisconsin Card Sorting (Berg, 1948); Trails B (Spreen and Strauss, 1991); Stroop (Interference trial); (Spreen and Strauss, 1991).
Psychomotor efficiency	Grooved Pegboard task; Response Inhibition task.
General intelligence	Verbal IQ score; Vocabulary and Block Design tasks.

See References [23] and [62] for details about the performance of diabetic subjects in each test, as compared to controls.

patients. The age of onset of diabetes mellitus and the quality of glycemic control are possibly the two most important ones. In a population of children with T1DM evaluated 6 years after disease onset, those who developed T1DM at less than 4 years of age had impaired executive skills, attention, and processing speed when compared with those who were diagnosed after 4 years of age [38]. The 'early-onset effect' has been attributed to the adverse effects of metabolic disturbances on the developing brain and appears to persist through adulthood [43].

Adequate glycemic control also appears to be importantly associated with cognitive performance in patients with T1DM. Psychomotor abilities, motor speed [30,44], attention, memory, verbal IQ scores [45–47], and academic achievements [46] are improved with better glycemic control [47]. On the Diabetes Control and Complications Trial (DCCT) patients with T1DM with mean serum glycated hemoglobin (HbA1c) lower than 7.4% performed significantly better on tests of motor speed and psychomotor efficiency than those subjects which mean HbAlc greater than 8.8% during the 18-year follow-up [44]. In addition, patients with acute hyperglycemia perform worse on tests of cognitive function, showing increased number of mental subtraction errors, loss of inhibition and focus, impaired speed of information processing, decreased attention, and impaired working memory [48,49]. Conversely, no association between multiple severe episodes of hypoglycemia and impaired cognitive function in patients with T1DM was found in the DCCT [44].

In a metanalysis, the presence of other diabetic complications was associated with poorer cognitive function in most studies involving T1DM patients [40]. Deficits in fluid intelligence, information processing speed, attention, and concentration have been associated with the presence of retinopathy [50]. Whereas complications like retinopathy and nephropathy usually require years of diabetes before becoming clinically apparent, the onset of cognitive impairment has been found to occur earlier in the course of disease among T1DM patients [36]. Among children with T1DM, deficits in cognitive function have been detected as early as 2 years after diagnosis. In the follow-up, these children experienced less increase in general intelligence, vocabulary, block design, processing speed, and learning in general [36]. Proliferative retinopathy, macrovascular complications, hypertension, and duration of diabetes were associated with poorer performance on tests measuring psychomotor speed and visuoconstructional ability [30,31,39]. In another study, the occurrence of distal symmetrical polyneuropathy was related to worse cognitive function on most domains, except for memory [30].

2.2. Type 2 diabetes

Patients with T2DM have also been found to have specific and global cognitive deficits characterized by decreases in psychomotor speed [51,52], complex motor functioning [52], executive functions [52–54], memory skills [53–55], processing speed [55], immediate and delayed recall [56], verbal fluency [52, 57], attention [58] and visuospatial abilities [59]. Another neurocognitive dysfunction frequently observed in patients with T2DM is (vascular) depression, which is twice more common in these patients than among controls [60]. Besides sharing a common neurovascular pathogen with cognitive dysfunction, depression is also a cause of cognitive dysfunction by itself, since it may severely impairs attention [53,60,61]. A comparison in the cognitive performance between T1DM and T2DM is summarized in Table 1 and the neurocognitive tests utilized on these studies are shown on Table 2.

Cross-sectional studies evaluating cognition in T2DM patients demonstrate that immediate noncontextual, verbal memory, processing speed, and brief cognitive screening measures are much worse in diabetic patients than among controls [62]. Six out of 11 population studies demonstrate that T2DM patients are more likely than controls to show poor performance on brief cognitive screening measures. All the other measures were less likely to show significant differences between well-treated type 2 diabetic patients and controls. Taken together, the results of well-controlled cross-sectional populational studies demonstrate that findings across all evaluated neuropsychological measures are inconsistent [62].

Longitudinal studies, however, almost universally reveal a higher risk of dementia or significant cognitive decline in diabetic populations [9,63]. Studies with cognitive screening instruments or batteries of more comprehensive neuropsychological tests show that the rate of cognitive decline due to aging is increased 1·5-fold to 2·0-fold in individuals with T2DM [64], albeit a study of cognitive function in the oldest old (age at study entry 85 years) did not find any significant association between T2DM and accelerated cognitive decline [65,66]. This particularity among the oldest-old population may be a form of 'survivor effect', in which T2DM people with more advanced vascular burden already died from myocardial infarction, stroke, or even dementia or obesity-associated neoplasms [65]. Besides, as most westerners start to lose weight after middle age is over, many people above 80 might actually improve their T2DM control by losing weight. Alternatively, people with neoplasms or dementia may start to importantly lose weight even before the diagnosis of such conditions [65]. This phenomenon, however, is not to be confused with the fact that mild-moderate caloric restriction (30%) through life extends lifespan in invertebrates and vertebrates, including primates and, probably, humans [67]. Among the main mechanisms by which caloric restriction extends lifespan seems to be the facts that it (1) increases insulin sensitivity and (2) decreases the formation of AGEs and (3) ROS, resulting in less oxidative stress [67].

The risk of Alzheimer's disease (relative risk [RR] 1·5–27·0) and vascular dementia (RR 2·0–2·5) is increased in T2DM [66]. If we assume the prevalence of T2DM to be about 15% in people older than 60 years, a RR of 1·5–2·0 translates into a diabetes attributable risk for dementia of 7–13% [6]. This increased risk remains significant even after adjusting for the presence of other vascular risk factors [68]. Alzheimer's disease is by far the most common cause of dementia among people with T2DM. In fact, among all incident cases of dementia occurring in people with T2DM, Alzheimer's disease is the diagnosis in about 82.5% [20] to 91% of the situations [19].

As stated above, the enhanced risk for developing AD in diabetic patients remains strong even when vascular factors are controlled for, suggesting an importance of non-vascular mechanisms for AD pathogenesis [69]. Several factors might contribute to the increased AD risk in diabetes mellitus, including defects in insulin signaling, accumulation of pathological Aβ, and hyperphosphorylated Tau [70]. Some studies have shown that the association between diabetes mellitus and Alzheimer's disease is particularly strong among Apolipoprotein E epsilon-4 allele (APOEε4) carriers. Indeed, individuals with T2DM who possess the APOEε4 allele have twice the risk of developing Alzheimer's disease, as compared with non-diabetics subjects with the APOEε4 allele [70]. Brain pathology from T2DM patients frequently includes heavy deposition of β-amyloid and Neurofibrilary Tangles (NFTs) [69]. Moreover, amyloid deposition is markedly increased in individuals with both diabetes and the APOEε4 genotype [70,71].

Glycemic control appears to play an important role in preserving cognitive performance among patients with T2DM [72]. In patients with T2DM, studies have demonstrated an inverse relationship between serum HbAlc and working memory [53,54], executive functioning [53], learning [52], and complex psychomotor performance [52,73]. This finding supports the hypothesis that an inadequate glucose control is associated with worsening cognitive function. Another important finding is the association between both the duration and severity of T2DM at one side, and the degree of central (brain) and peripheral nervous system involvement, as demonstrated by decreased cognitive function and peripheral neuropathy, respectively [51, 54, 58]. Insulin-dependent T2DM subjects had

a higher risk of major cognitive decline than those with an adequate metabolic control only with oral hypoglycemiants [74].Conversely, repetitive episodes of moderate to severe hypoglycemia have been implicated as one possible etiology for long-term cognitive dysfunction in T2DM [73], even though the strongest evidence for memory disturbances is for the short period in which the subject is hypoglicemic [75,76].

3. Neuroimaging in diabetes

Several studies on the cerebral structure of patients with T1DM and T2DM have evidenced cortical and subcortical atrophy, besides increased leukoaraiosis (WMHLs), which were associated with impaired cognitive performance even after controlling for cardiovascular risk factors such as hypertension [14,15,77]. A strong interaction between diabetes and hypertension was observed, such that when the two conditions are present together, they result in a multiplicative greater risk for cortical brain atrophy [78]. A study involving elderly subjects have also found that hippocampus and amygdala atrophy were more pronounced in persons with T2DM [79]. Interestingly, after further adjustment for classical vascular risk morbidity, these results remained statistically significant. However, a similar study in subjects with T1DM failed to identify significant reductions in hippocampal and amygdala volumes, although these subjects did present mild ventricular enlargement and slight global cerebral atrophy [80].

Population-based studies indicate that diabetes is a risk factor for silent and symptomatic brain infarcts seen with MRI [81,82]. The presence of microvascular complications is associated with both reduced cognitive performance [50] and accelerated cognitive decline [31]. In patients with T2DM, WMHLs and subcortical/periventricular atrophy have been associated with reduced performance on tests of attention, executive function, information processing speed, and memory [15,83].

Diabetes severity and glycemic control may influence the degree of brain's lesion involvement. Some studies which have included elderly people in poor glycemic control found impairments in psychomotor efficiency and memory associated with WMHLs and subcortical brain atrophy [15]. Among well-controlled T2DM of less than 10 years duration, deficits on hippocampal-based memory performance and selective MRI atrophy of the hippocampus were found in comparison with age-matched controls [84]. Among these well-controlled individuals, HbA1c serum levels were inversely related to head-size adjusted hippocampal volumes. Higher HbA1c levels were also correlated with lower gray matter density in important areas for language, memory, and attention [85]. Higher HbA1c levels were also associated with reductions of gray matter in the right cuneus and precuneus regions, and reductions of white matter in the right posterior parietal region [86]. In addition, the occurrence of hypoglycemia in both T1DM and T2DM groups was correlated with increased cerebral atrophy in several cerebral regions, more specifically in certain areas of the frontal and temporal lobes, besides the thalamus [85,86,87].

Some other studies have been shown that the presence of peripheral diabetic complications is more associated with lesions of certain specific cerebral areas [83,86]. For example, T1DM patients with proliferative retinopathy had decreased gray matter density in the right inferior gyrus and right occipital lobe. They also presented significantly smaller white matter volume compared with those patients with diabetes but no retinopathy [86]. The occurrence of small, punctate, white-matter lesions is higher in patients with retinopathy than in those without it [50].

4. Pre-diabetes and the metabolic syndrome (MetS)

Healthy individuals are able to maintain their plasma glucose levels constantly around 4–5 mM and, when blood glucose rises following meals, the insulin secreted by the pancreas also rises to maintain normal glycemia [1]. Insulin regulates the uptake of glucose by the tissues and it storage as glucogen. The major sites of insulin action are the liver, fat tissue, skeletal muscle and the brain, in special some regions with a high demand for glucose [1]. When sensitivity to insulin is reduced on these tissues, this is termed insulin resistance (IR). The occurrence of IR combined with a pancreatic insufficiency to provide enough and prompt insulin secretion to maintain euglycemia is termed T2DM. The term 'pre-diabetes' is employed when, in the presence of IR, enough insulin is still produced to prevent overt diabetes, but it results in impaired fasting glucose and/or impaired glucose tolerance [1,19,20].

In pre-diabetes, body tissues are exposed to abnormally high levels of insulin for extended periods, what may persist for many years/decades. Hyperinsulinemia seems to be implied in neurodegeneration and cognitive decline [19,20]. The hypothesis that diminished glucoregulatory control is related to decrements in cognitive performance is supported by studies which evaluated neuropsychological performance among pre-diabetic adults [20]. Impaired glucose tolerance and hyperinsulinemia were associated with reduced Mini Mental State Examination (MMSE) scores [87] and have also been linked to increased risk for mild cognitive impairment (MCI). Subjects with MCI are at increased risk for dementia [20,88]. Interestingly, some studies have demonstrated that patients with impaired glucose tolerance may have the same pattern and severity of cognitive deficits as patients with T2DM [89]. In another study, reduced glucose tolerance was associated with decreased general cognitive performance, memory deficits, and hippocampal atrophy on the MRI [90]. Multiple investigations on patients with impaired glucose tolerance have shown them to have lower MMSE and long-term memory scores [91], impaired verbal fluency [57], increased risk for Alzheimer's disease [92], and increased odds for vascular dementia [93], as compared with control subjects. However, not all studies found that patients with pre-diabetes perform worse than normoglycemic individuals [58,94–96].

Impaired glucose tolerance is one component of MetS, together with central obesity, hypertension, hypertriglyceridemia and reduced HDL-cholesterol. Each component of the MetS has been shown to be an independent risk factor for stroke, but hyperglycemia might be more important than the other components in the pathogenesis of both peripheral and central neuropathy [97]. Our group has recently evaluated 422 community-dwelling elderly ($\geq$60) in Brazil, in order to investigate the association between cognitive impairment and the frontal-subcortical (geriatric) syndrome (FSCS), at one side, and MetS in the other side. FSCS, which is caused by ischemic disruption of the frontal-subcortical network, was defined as the presence of at least one frontal release sign (grasping, palmomental, snout, or glabellar) plus the coexistence of $\geq$3 the following criteria: (1) cognitive impairment, (2) late-onset depression, (3) neuromotor dysfunction, and (4) urgency incontinence. We found that MetS was significantly associated with FSCS (OR = 5.9; CI: 1.5–23.4) and cognitive impairment (OR = 2.2; CI: 1.1–4.6) among stroke-free subjects [22].

Obesity is associated with a significant reduction in insulin sensitivity, as insulin sensitivity inversely correlates with Body Mass Index (BMI) [98]. With the worldwide rapidly increasing prevalence of obesity, there is a corresponding increasing prevalence of insulin resistance and pre-diabetes [98,99]. Fifty percent of adults have central obesity and the occurrence of central obesity in midlife increases the risk of dementia independent of diabetes and cardiovascular comorbidities [100]. Generalized brain atrophy and regional alterations in gray matter volume occur in obese male subjects, suggesting that subjects with a high BMI are at greater risk for cognitive decline [101].

5. Pathophysiologic mechanisms

Mechanisms underlying the development of nervous system lesions and cognitive dysfunction in patients with disturbances in the insulin homeostasis have not been completely elucidated. There

are supporting evidence from many hypotheses in explain the pathophysiology of neurodegeneration associated with diabetes, prediabetes, and MetS [98, 99]. The main hypotheses pointing to the potential implied mechanisms involves hyperglycemia, hypoglycemia, (micro)vascular disease, insulin resistance, and hyperinsulinism, all which are well-represented by the concept of MetS (Fig. 1). Besides, the MetS construct includes central obesity, hypertension, and dyslipidemia, all of which are related to hyperinsulinism [98]. The above three other components of MetS are not necessarily present in (pre)diabetes [98, 99], but are also important risk factors for cognitive dysfunction [22]. The possibly involved mechanisms relating these other MetS components to cognitive dysfunction are not fully discussed in this review, but are also cited in Fig. 1.

Many cognitive dysfunctions associated with metabolic syndrome may have their common pathophysiologic mechanism unified by invoking the concept of the FSCS (22; see item 4, penultimate paragraph).

5.1. Hyperglycemia

Glucose is the main energy substrate of the human brain; however the occurrence of chronic hyperglycemia can be deleterious for the brain [102]. The brain, which constitutes only 2% of the human body weight, utilizes almost 25% of total body glucose [102]. The glucose metabolism is used not only for energy substrate but also the breakdown of glucose provides important compounds for neurons, including neurotransmitters such as acetylcholine and glutamate [103]. Several studies have shown that hyperglycemia has toxic effects and can lead to slowly progressive functional and structural abnormalities in the brain [10]. Chronic hyperglycemia could, thus, be one of the determinants of cognitive decline in people with abnormal glucose metabolism [104,105].

The deleterious effects of hyperglycemia are mediated through an increased flux of glucose through the polyol and hexosamine pathways, disturbances of intracellular second messenger pathways, an imbalance in the generation and scavengers of ROS, and by AGEs [106]. Besides being directly implied in aging (last two processes), these phenomena also contributes to microvascular changes, what leads to microinfarcts and generalized brain atrophy/WMHL, which, in turn, result in cognitive decline and dementia [10,107,108]. Three mechanisms that mediate the toxic effects of hyperglycemia/hyperinsulinemia are responsible for the aging process of the brain, namely: (1) accumulation of AGEs; (2) increasing formation of ROS, with consequent increased oxidative stress; and (3) microvascular pathology [23,108,109]. Thus, these effects on cognition and brain structure might be responsible for the "accelerated brain aging" that occurs in subjects with diabetes [23,110].

The finding of accelerated brain aging in DM is confirmed by experimental models in rats [111]. Alterations include neuroanatomical and neurochemical changes, impairments in stress reactivity and hypothalamic–pituitary–adrenal axis activity, as well as deficits in insulin signaling and neuroplasticity. Some studies have shown that RAGEs, galectin-3 (a proatherogenic molecule), and the polyol pathway activation were all increased in diabetic rat brains, whereas activity of the glycolytic enzyme glyceradehyde-3-phosphate dehydrogenase was decreased, indicating elevated superoxide levels [112]. Neuronal apoptosis and suppression of cell proliferation/neurogenesis are observed in the hippocampus of diabetic rodents. Nuclear factor B transcription factors, a proinflammatory gene marker up-regulated by AGEs, and S-100 protein, a marker for brain injury that can bind to RAGEs, were both up-regulated in the hippocampus of diabetic rats [113–116]. These data suggest that insulin resistance, hyperinsulinism and hyperglycemia, causing accumulation of AGEs and ROS, may trigger a cascade of events that leads to neural aging and hippocampal atrophy, which may represent the initial neuronal damage in diabetes mellitus [117].

In addition, neurochemical changes have also been observed and may contribute to cognitive dysfunction. Insulin resistance impairs long-term potentiation, a fundamental mechanism for memory consolidation [118]. Other, neurotransmitter functions which are altered in diabetes mellitus include decreased acetylcholine production [119], decreased serotonin turnover, decreased dopamine activity, and increased norepinephrine [120,121].

5.2. Hypoglycemia

A common and feared side effect of diabetes treatment is hypoglycemia. The risk of hypoglycemia is a barrier to achieving and

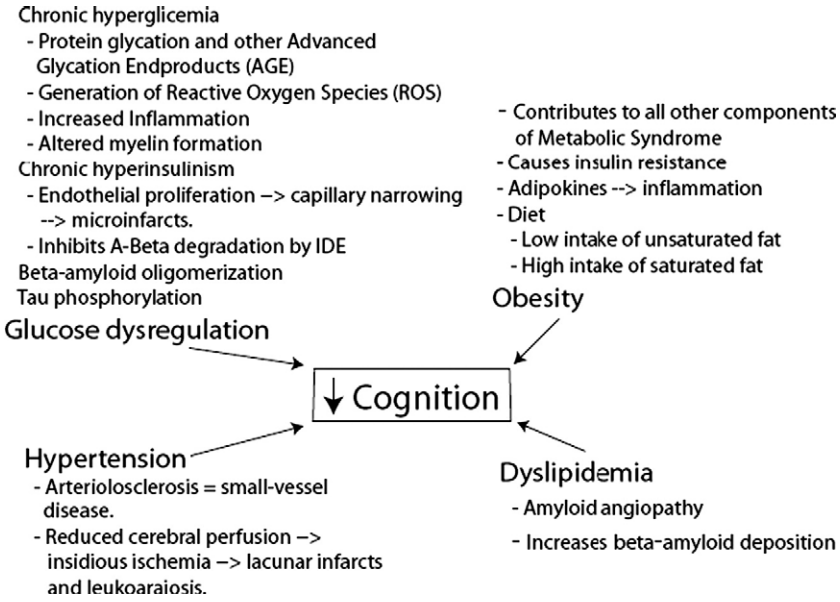

Fig. 1. Key components of the Metabolic Syndrome (MetS) and their possible pathophysiological links with cognitive decline. All MetS components may contribute for atherosclerosis (see Ref. [226]). Obesity, especially central obesity is a key component for the development of the other constituents of the syndrome. Aging is associated with increased insulin resistance, and may aggravate the severity/control of most components of the MetS. Hypoglycemia is not represented here (see text). Many cognitive dysfunctions associated with metabolic syndrome may have their common pathophysiologic mechanism unified by invoking the concept of the 'frontal-subcortical geriatric syndrome' (Ref. [22]; see text, item 4, penultimate paragraph).

maintaining optimal glycemic control. It is widely recognized that prolonged and severe hypoglycemia may leads to permanently brain damage, besides its immediate effects on the brain which acutely affects cognition, mood, and conscious level [122,123,124]. What remains controversial is if repeated minor episodes of hypoglycemia may contribute to cognitive dysfunction [125]. Hypoglycemia also exerts profound effects on various constituents of the blood and the vasculature. Although the effects are transient and unlikely to exert any long-term consequences on a healthy circulation, the potentially deleterious effects on a damaged vasculature should be considered. Recurrent exposure to hypoglycemia may exert an important adverse effect when the vasculature has already become compromised by macro- and microangiopathy [126].

In the presence of hypoglycemia, several responses occur within the brain, including activation of the central sympathetic nervous system, promoting physiological changes manifested as autonomic symptoms such as sweating, tremor, a pounding heart, hunger, and anxiety [127,128]. Cognitive dysfunction is experienced subjectively in the form of neuroglycopenic symptoms, including difficulty in concentrating, drowsiness, and incoordination [128]. Perception of these symptoms warns the patient, who prompt action is required to treat the hypoglycemia and restore blood glucose to normal levels. Most cognitive modalities are impaired when blood glucose falls below 2.8 mMol/L. Tests that require mental speed and that are complex or demand a high level of attention are affected most, while tests of simple motor function and reaction time are relatively preserved [129].

Recurrent severe hypoglycemia may occasionally cause sub-clinical cerebral injury or permanent cognitive impairment [130,131]. In these cases, human autopsy studies have shown laminar, multifocal or diffuse necrosis and gliosis of the cerebral cortex and chromatolysis of ganglion cells [132]. The regions more vulnerable to hypoglycemia include the cortex, basal ganglia, and hippocampus [123]. In addition, there is a possible relationship between early nocturnal hypoglycemia during sleep (a time in which consolidation of memories occurs), and cognitive dysfunction [133]. Conversely, most studies have not shown neurocognitive deficits associated with nocturnal hypoglycemia induced later during the sleeping period [134,135].

5.3. Vascular disease

Diabetic patients have an increased risk of developing cerebrovascular disease, and many have established micro- and macrovascular complications of varying severity. Cerebrovascular disease related to diabetes mellitus is more pronounced in the older age group [63]. It is now well recognized from studies using both animal and human models that atherogenesis contains a significant inflammatory component, which contributes to its progression and to the subsequent emergence of thrombotic complications [136]. This has shifted the focus of research from an examination of traditional cardiovascular risk factors to the investigation of processes that involve the vasculature at a molecular level. These molecular processes preferentially affects cells that are directly implicated in atherogenesis, such as endothelial cells, macrophages, monocytes, platelets and smooth muscle cells [136].

Diabetes mellitus is an important risk factor for stroke and is also one of the most consistent predictors for recurrent stroke or for stroke after a Transient Ischemic Attach [137,138]. This diabetes-related increased risk for recurrent stroke ranges from 2.1 to 5.6 times the risk of nondiabetic patients [139,140], and is independent of glucose control during the interstroke period [141]. Diabetes and impaired glucose tolerance have been associated with increased Carotid Intima-Media Thickness (CIMT) [142,143]. Diabetic patients who have a stroke have significantly greater CIMT than both diabetic subjects without stroke and nondiabetic patients [144,145]. Carotid Intima-Media Thickness is directly related to the duration of diabetes and glucose control, as evidenced by the Insulin Resistance Atherosclerosis Study [146].

Some studies have demonstrated the existence of a basal chronic systemic inflammatory state associated with endothelial dysfunction, platelet hyperactivity, and microvascular complications of retinopathy and nephropathy in diabetic patients [147–149]. In the EURODIAB prospective complications study, inflammatory markers like C-reactive protein, interleukin-6 and tumor necrosis factor-α were found to be strongly and independently associated with vascular disease in people with T1DM [150]. Even in the absence of vascular complications, surrogate markers of endothelial dysfunction, including C-reactive protein, vonWillebrand factor and vascular cell adhesion molecule-1 are elevated in T2DM patients [151,152]. Moreover, plasma concentrations of the anti-inflammatory cytokine interleukin-10 are lower in people with type 2 diabetes [153].

Macrovascular and microvascular disease both cause significant morbidity and mortality in people with diabetes mellitus. Thickening of capillary basement membranes, the hallmark of diabetic microangiopathy, has been found in the brains of patients with diabetes [154]. These patients have a 2- to 6-fold increased risk for thrombotic stroke. Vascular disease has long been hypothesized to contribute to abnormalities in cognition [122]. Macrovascular disease is not only more common, but is more aggressive and widespread in people with diabetes than in non-diabetic subjects [155]. While this vascular outcome occurs both in T1DM and T2DM, its magnitude and severity is significantly greater in T2DM due to the co-existence of multiple cardiovascular risk factors, including hypertension and dyslipidemia. Conversely, autopsy studies of patients with long-standing T1DM have shown important changes possibly related to microvascular disease, including diffuse brain degeneration, pseudocalcinosis, demyelination of cranial nerves and spinal cord, and nerve fibrosis [156,157].

Patients with DM have also been found to have decreased global rates of cerebral blood flow, which is correlated with disease duration. The association of ischemia and hyperglycemia may be more detrimental to the brain. Even modestly elevated blood glucose levels during a cerebrovascular event may contribute to greater infarcted areas [158]. Two possible mechanisms to explain the synergism between hyperglycemia and ischemia are lactate and glutamate accumulation. Hyperglycemia provides more substrate for lactate to form, worsening cellular acidosis, and providing accumulation of glutamate, which is also a strong neurotoxic neurotransmitor at very high concentrations [122,159,160].

Diabetes mellitus is associated with a hypercoagulability state which is characterized by increased concentrations in anti-fibrinolytic and other procoagulant factors, as well as by alterations in Nitric Oxide (NO) metabolism. This hypercoagulability is associated with enhanced risk for thrombotic vascular events [161–163]. Plasminogen activator inhibitor-1 and antithrombin III, which inhibit fibrinolysis, as well as the tissue plasminogen activator antigen, a marker of impaired fibrinolysis, were consistently found to be elevated in IR phenotypes [164–166]. Some studies have further suggested that procoagulant factors, such as factor VII, factor VIII, and the von-Willebrand factor also rise with the degree of insulin resistance [161,167]. Another important mechanism of diabetes hypercoagulability is platelet hyperreactivity. Studies in diabetic patients have found an increased status for platelet aggregation, which is explained by increased platelet response to ADP and elevation of thromboxane A2 concentrations [168,169]. This enhanced response to ADP may be mediated by the upregulation of GPIIb-III receptors and by the failure of insulin-induced inhibition of platelet aggregation that occurs in DM [170,171]. Patients with (pre)diabetes have also decreased endothelium-dependent vasodilatation; a consequence of either decreased NO production or impaired NO metabolism [172–174].

5.4. Insulin resistance, tau hyperphosphorylation, and the amyloid cascade

Besides being a modulator of food intake and energy homoeostasis, insulin is, also an important neurothrophic factor [176–181]. It

modulates brain activity, above all for such high glucose demanding functions such as memory. AD patients were found to have lower than normal CSF levels of insulin [181]. How can clinical hyperinsulinism be a risk factor for AD whereas lab experiments evidence insulin to be an important neurothrophic factor? These two apparent paradoxal findings may be reconciliated by evoking the concept of insulin resistance. Whereas insulin is clearly neurothrophic at moderate concentrations, too much insulin in the brain may be associated with reduced amyloid-β (Aβ) clearance due to competition for both principal depurative mechanisms — the Insulin-Degrading Enzyme (IDE) [178]. Since IDE is much more selective for insulin than for Aβ, brain hyperinsulinism may deprive Aβ of its main clearance mechanism [178].

Insulin crosses the blood-brain barrier, and might even be produced locally in the brain, exerting its effects on cells by binding to a specific cell surface receptor [180,181]. Insulin receptors are distributed throughout the brain, being abundant in the hippocampus and the cortex [182]. Binding of insulin to its receptor activates the intrinsic tyrosine kinase activity of the cytoplasmic domain of the insulin receptor. This leads to autophosphorylation of tyrosine residues, what initiates several intracellular signaling cascades [183–185]. In the brain, insulin influences the release and reuptake of neurotransmitters, and also appears to improve learning and memory [186]. The initial components of the insulin receptor signaling cascade in the brain are largely similar to those of the periphery [186,187]. The downstream targets of the cascade are quite different, however, probably involving neuronal glutamate receptors, among others [186].

Insulin receptor-mediated signal transduction controls the activity of several enzymes in a cascade-like manner. Phosphatidylinositol 3-kinase (PI3K) is insulin-regulated and activates protein kinase B (PKB, also known as Akt) [188,189]. PIP3 recruits PKB, to the plasma membrane, where it is phosphorylated and activated by specific protein kinases [190]. PKB has many important cellular targets including glycogen synthase kinase 3 (GSK3). Phosphorylation of the N-terminal region of GSK3 by PKB causes inactivation of GSK3, reducing the phosphorylation of glycogen synthase (GS). Dephosphorylated GS is the active form of the enzyme. The active GS increases the rate of conversion of glucose 6-phosphate to glycogen. This pathway links the insulin receptor at the cell surface with enzymes of glycogen metabolism within the cell [191]. In this way, GSK3 generally opposes the actions of insulin. Thus, GSK3 inhibits glycogen synthesis, glucose uptake, and also alters the expression of genes regulated by insulin [192].

Glycogen synthase kinase 3 is highly expressed in all eukaryotes cells and is involved in a number of physiological processes ranging from glycogen metabolism to gene transcription [193]. There are two isoforms of the enzyme that are ubiquitously expressed in mammals: GSK3α and GSK3β [193,194,195]. There is evidence that GSK3 plays a central role in AD, and that its deregulation accounts for many of the pathological hallmarks of the disease in both sporadic and familial AD cases, leading to formulation of the 'GSK3 hypothesis of AD' [196]. Glycogen synthase kinase 3 is implicated in the hyperphosphorylation of tau, increased production of β-amyloid and in inflammatory responses. Glycogen synthase kinase 3 also reduces acetylcholine synthesis and is a key mediator of apoptosis. These findings are in accordance with alterations present in AD, including cholinergic deficit, memory impairment and neuronal loss [197,198].

There is increasing evidence linking insulin resistance to cognitive decline and dementia in diabetes [24,199]. There are alterations in cerebral insulin receptor signaling, leading to a cerebral insulin resistant state. Alterations in brain's insulin and its receptor may disrupt glucose homoeostasis and affect amyloid metabolism. The formation of AGEs and ROS may play an important role in translating insulin resistance into amyloid deposition and tau phosphorylation [25,26]. Indeed, cerebral insulin resistance has been implicated in accumulation of amyloid-β-peptide (Aβ) and tau protein, which are the main components of senile plaques and neurofibrillary tangles (NFTs), respectively. These two neuropatholical features are the pathological hallmark of Alzheimer's disease [25,175]. One hypothesis to explain the above relationships is that GSK3 activity might be enhanced in patients with insulin resistance, representing a possible link between insulin resistance and Alzheimer's disease [200,201].

Several studies point to an intriguing relationship between diabetes mellitus and Alzheimer's disease. Patients with AD have lower Cerebrospinal fluid insulin levels and reduced insulin-mediated glucose disposal when compared to healthy control subjects [202,203]. While there is very little insulin mRNA in the brain, recent ultra-sensitive PCR data show that insulin message can be detected in postmortem human brain, being reduced in AD brains. This finding leaded the authors to suggest that Alzheimer's disease could be a "type III diabetes" due to a marked reduction in CNS insulin concentrations [181,204]. In addition, knockout of the insulin receptor gene is not sufficient to cause cognitive deficits or neurodegeneration even though some regions show enhanced GSK3β activity [205]. The observation that activation of the insulin receptor was impaired in brain autopsy samples of AD patients, has given rise to the notion that Alzheimer's disease could be qualified as "an insulin resistant brain state" [206].

Another important link between insulin resistance and the amyloid cascade may be related to the IDE. Insulin degrading enzyme is a metalloprotease enzyme responsible for insulin degradation and is also the main enzyme responsible for Aβ degradation [178]. Insulin degrading enzyme is secreted to the extracellular space by microglial cells in the brain, where it degrades Aβ peptide, leading to reduced Aβ peptide concentration in the brain, thus reducing aggregation and plaque formation [207]. Insulin degrading enzyme levels have been reported to be decreased in the brains of AD patients [208,209], especially in the hippocampus [210]. It has also been hypothesized that hyperinsulinemia in people with pre-diabetes and T2DM effectively sequesters IDE, reducing Aβ peptide degradation. This would increase levels of Aβ peptide, and promote many of the pathological features associated with Alzheimer's disease. Supporting this model, the affinity for the binding of insulin to IDE is much greater than the one for the Aβ peptide [211].

In patients with Alzheimer's disease, IDE expression in the hippocampus is substantially reduced, relative to controls, in particular among patients with the APOEε4. This latter observation could explain the potential interaction between diabetes and the APOEε4 genotype in multiplying the risk of dementia [209]. Curiously, although the presence of the APOEε4 is associated with an increased incidence of Alzheimer's disease [212], it seems that insulin resistance is only a significant risk factor for AD in those patients without APOEε4 [90,202]. Subjects with AD without the APOEε4 had also improved memory scores in the setting of hyperinsulinemia, which was not the case for people with at least one APOEε4 allele [213,214]. However, in the Honolulu-Asia Aging Study, those subjects with both T2DM and the APOEε4 allele had an additive increased risk of dementia and Alzheimer's pathology [8]. In despite of this apparent contradiction, it seems that IR, T2DM and APOEε4 are distinct risk factors for the development of Alzheimer's disease, a hypothesis that is supported by the fact that those with diabetes had a lower prevalence of the APOEε4 [215].

6. (Pre)diabetes and non-age-related psychiatric diseases

The relationship between pre-*diabetes*/*diabetes mellitus* and some non-age-related psychiatric diseases go beyond the scope of this review. We could not, however, let unmentioned that patients with mental illnesses such as schizophrenia, schizoaffective, and bipolar disorders have an increased prevalence of metabolic syndrome and *diabetes mellitus* — as compared with the general population [216].

The high prevalence of metabolic syndrome in schizophrenic patients has assumed greater significance since the increasing use of second-generation antipsychotics. These drugs have been associated

with substantial weight gain, a major risk factor for glucose metabolism abnormalities [217]. Conversely, several studies [218,219,220] have been suggesting that schizophrenia is associated with abnormal glucose metabolism independently of antipsychotic use. In addition, some studies have suggested that first-degree relatives of schizophrenic patients are at increased risk of diabetes [221]. These findings suggest schizophrenia might also be associated with abnormalities in glucose metabolism, regardless of the use of antipsychotics [222].

7. Conclusions

The present review reinforces the view that diabetes is strongly associated with multiple alterations in the proper functioning of the brain. T1DM and T2DM. An important and common complication of both T1DM and T2DM is cognitive dysfunction. As expected, however, the specific alterations in cognitive abilities between the two types of diabetes do not completely overlap. In patients with T1DM, specific and global deficits evolving speed of information processing, psychomotor efficiency, attention, mental flexibility, and visual perception seem to be present, whereas in patients with T2DM, an increase in memory deficits, a reduction in psychomotor speed, and a reduced frontal lobe/executive function have been found. Differences in methodology across studies, including inadequate sample sizes, difficulty in identifying valid control groups and differing test sensitivities, may account for the variability in these findings between the two main types of DM. Alternatively, hyperinsulinemia and comorbidities (MetS components) in T2DM, but not in T1DM, might be contributing to some of these differences.

It is also important to consider the age of onset of the diabetes, the glycemic control status, and the presence of diabetic complications. The impact of diabetes on cognitive functions seems to be greater in older people with worse glycemic control and long duration of the disease.

Neuroimaging studies also highlighted several structural cerebral changes that occur in association with DM. Many populational studies have shown that DM is a risk factor for (silent) cerebral infarcts and is associated with a slight degree of cortical and subcortical atrophy. Most MRI studies revealed an association between DM and the occurrence of lacunar infarcts and WMHLs. In line with observations from studies of cognitive function in DM, findings from populational studies also indicate that poorer glycemic control is associated with accelerated cerebral atrophy. The degree of cortical atrophy encountered in DM subjects suggests that diabetes may also have global, non-vascular effects on the brain. Alternatively, small-vessel disease may contribute for this generalized brain atrophy frequently found in DM individuals. Several molecular and biochemical experiments in cellular and animal lab models also supports the hypothesis that mechanisms other than vascular disease are involved in the increased risk of AD in DM.

Many studies have revealed that people with pre-diabetes also are at increased risk for developing adverse anatomical and functional brain changes. As a consequence, mild cognitive decline may develop even before of the installation of frank diabetes. Neuropsychological profile of individuals with impaired glucose tolerance appears to mimic what is typically observed in individuals with age-associated memory impairment. However, not all studies found that patients with pre-diabetes perform worse than normoglycemic individuals. Given that cognitive impairment is not invariably found in older diabetic patients, it is necessary to understand the factors that lead to cognitive impairment and the other ones that protect from DM-associated neurodegeneration.

The underlying neuropathologic changes associated with DM have been described to be very similar to the ones usually associated with 'pure' aging. In fact, DM is probably strongly associated with an accelerated biological aging. Central neurological complications associated with DM include an increased risk for dementia of both vascular and Alzheimer's type. However, there are few detailed epidemiological studies considering specific vascular risk factors vis-à-vis the risk in developing Alzheimer's, Vascular, or mixed-type dementia. Studies involving large population-based cohorts of elderly people with pre-diabetes and DM, accessing the progress of (pre) diabetes, MetS, vascular disease, and cognition are necessary. Accelerated brain aging and disturbances of insulin metabolism in the brain may be additional factors that link DM to AD. This hypothesis should be tested in prospective studies that include measures of amyloid and tau-protein metabolism.

8. Perspectives

The establishment of a close relationship between insulin resistance and Alzheimer's disease could open a large vein for the development of novel preventive and therapeutic interventions for these conditions. One possible future direction that might arise in studying the molecular changes that occur in the brain in the presence of insulin resistance is the elucidation of the pathophysiology of the AD. Besides, the discovery of the most important link(s) between DM and AD would be of extreme importance. Assuming that insulin resistance is the main mechanism involved in neurodegeneration, studies utilizing available drugs to improve insulin sensitivity, such as metformin and the thiazolidinediones [223]. However, there is as yet no evidence that they can decrease the risk of cognitive decline besides and beyond their hypoglycemiant effect [223]. New methods like the application of intranasal insulin, which is able to quickly pass through the blood-brain barrier, are also promising [224], but results are still conflicting [225]. Therefore, more research is need before intranasal insulin and insulin sensitivity enhancers can be considered useful in preventing and treating cognitive dysfunction, be it in the presence or not of disturbances in the blood glucose homeostasis.

Acknowledgement

None.

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