2014

Cognitive Impairment in Patients with Type 2 Diabetes Mellitus: Perspectives and Challenges

Okezie I. Aruoma

Darshini Narrain

Joseph Indelicato
Touro College, joseph.indelicato@touro.edu

Emmanuel Bourdon

Fatima Murad

See next page for additional authors

Recommended Citation

Aruoma, O. I., Narrain, D., Indelicato, J., Bourdon, E., Murad, F. & Bahorun, T. (2014). Cognitive impairment in patients with type 2 diabetes mellitus: Perspectives and challenges. Archives of Medical and Biomedical Research, 1(2), 79-89.

Published by iambr.info/AMBR

Open Access Review

Cognitive impairment in patients with type 2 diabetes mellitus: Perspectives and challenges

Okezie I Aruoma[1], Darshini Narrain[2], Joseph Indelicato[3], Emmanuel Bourdon[4], Fatima Murad[5] and Theeshan Bahorun[2]

To cite: Aruoma OI, Narrain D, Indelicato J, Bourdon E, Murad F, Bahorun T. Cognitive impairment in patients with type 2 diabetes mellitus: Perspectives and challenges. *Arch Med Biomed Res.* 2014;1(2):79-89.

Publication history
Received: March 3, 2014
Revised: May 8, 2014
Accepted: May 10, 2014

Correspondence to
OI Aruoma;
oaruoma@auhs.edu
T Bahorun;
tbahorun@uom.ac.mu

ABSTRACT

Type 2 Diabetes Mellitus is associated with elevated blood glucose level, abnormal abdominal fat deposition, insulin resistance and a number of complications including embryopathy, cardiovascular diseases, nephropathy, neuropathy, microangiopathy and retinopathy. Complications extending to the central nervous system may have a deteriorating effect on mental health including a decline in cognitive functioning. This could be a reason for depression, lack of compliance towards medication/treatment, and the inability of patients to meet the day-to-day management demands of the disease. Due to the high metabolic demand for energy in the brain, perturbations in glucose metabolism can noticeably impact cognitive performance. This review discusses and enlightens on the factors contributing to cognitive impairment in Type 2 Diabetes Mellitus. An understanding of the mechanisms of diabetes-related cognitive impairment and the resulting behaviors of patients can help healthcare professionals implement treatments to significantly improve health status and quality of life of patients with diabetes.

KEY WORDS: ***Type 2 Diabetes Mellitus; Cognitive Impairment and Brain Function; Insulin and Brain Function; Diabetes Therapeutic Drugs and Compliance; Depression and Alzheimer's Disease; Neuropsychopharmacology of Diabetes; Functional Foods and Human Diet; Quality of Life and Wellness***

INTRODUCTION

Diabetes mellitus remains a major global health problem impacted by genetic risk propensity. Whilst this makes it largely unpreventable, there exist preventive measures, which reduce the onset of the disease and the extent of the progression of associated complications in patients with diabetes[1]. Type 2 Diabetes is associated with the elevation of blood glucose level, abnormal abdominal fat deposition, insulin resistance and a number of complications including embryopathy, cardiovascular diseases, nephropathy, neuropathy, microangiopathy and retinopathy[2-4].

Complications of diabetes extending to the central nervous system lead to a range of alterations in brain functioning[5,6]. Diabetes-related cognitive impairment is a likely cause of depression and interference with a number of processes such as patient's non-adherence to medication/treatment, being

noncompliant (for example, patient's likelihood to participate in exercise programs and tendency to stay on appropriate diets) and inability to do primary self-care[7,8]. While the need to address why increasing numbers of people are suffering from diabetes abounds, it is also important to look into ways to help patients meet the day-to-day challenges of the disease, which may be derived through development of new treatments and management strategies[9]. An assessment of the levels of cognitive impairment in patients with diabetes will help to understand the behavior of patients towards medication, treatment, nutrition and to their lifestyle as a whole. Our research to define cognitive functions in Type 2 Diabetes patients is focused on the effects of dietary functional supplements like chocolate, fermented papaya preparation and tea (green and black tea) on cognitive performance and health management of the prediabetic, diabetic and ischaemic heart patients[10-12]. The outcome can be benchmarked with the assessment of the effects of available therapeutic drugs on cognition functioning as well as the assessment of the genetic relationship between diabetes and cognitive deficits[13]. The remarks of Perrin et al[14], that "People with diabetes and peripheral neuropathy have different illness schemata that may influence health-related behavior. Education aimed at improving foot-care behavior and foot-health outcomes should be tailored to specific illness schemata related to peripheral neuropathy", is of worthwhile interest for readers to refer to the context of the paper. In the study of Le Floch et al[15], it was found that in people with Type 2 Diabetes aged 70 years and older, retinopathy, nephropathy and peripheral neuropathy were associated with impaired geriatric scale scores. The study highlights the benefits of systematic assessment of cognition, autonomy, nutritional status and mood using geriatric scales in elderly people with diabetes. The prevention and management/treatment of diabetes-related cognitive deficits will not only lead to a better health status of patients but will ultimately improve their quality of life.

FACTORS CONTRIBUTING TO COGNITIVE IMPAIRMENT

In the metabolic integrity, aging process and perturbations caused by problems such as insulin resistance[16], chronic inflammation[17], oxidative stress[18], declining hormone levels[19] and endothelial dysfunction[20], result in physical deterioration of the brain and subsequent cognitive decline. The factors are discussed with emphasis on aging, insulin resistance, inflammation, oxidative stress and hormonal imbalance.

Aging

Aging is a gradual and complex process in which cells, tissues, organs and the whole organism itself deteriorates in a progressive and irreversible manner that, in the majority of cases, implies pathological conditions that affect the individual's quality of life. The process profoundly impacts the brain and causes deterioration of neuronal and mitochondrial membranes, which leads to the loss of cellular integrity and impaired neuronal function. Diabetes-related complications lead to acute alterations in mental status due to poor metabolic control as well as greater rates of decline of cognitive functioning with age[21,22], higher prevalence of depression[23] and increased risk of Alzheimer's disease[24,25]. Alzheimer's disease (AD), is characterized by dementia that typically begins with subtle and poorly recognized failure of memory and slowly becomes more severe and, eventually, incapacitating. The clinical diagnosis of AD is characterized by slow progressive dementia and gross cerebral cortical atrophy. The age-related declines in neurotransmitter synthesis and signaling, coupled with reductions in synaptic density and plasticity (adaptability), and loss of as much as 50%

of the length of myelinated axons make the brain increasingly less efficient with aging. As noted by Riddle[26], "The basic cognitive functions most affected by age are attention and memory. Neither of these are unitary functions, however, and some aspects of attention and memory hold up well with age while others show significant declines". Perception (often considered to be a precognitive function) also shows significant age-related declines attributable mainly to declining sensory capacities. Thus, deficits at these early processing stages could affect cognitive functions later in the processing stream. Higher-level cognitive functions such as language processing and decision-making may also be affected by age. These tasks naturally rely on more basic cognitive functions and will generally show deficits to the extent that those fundamental processes are impaired. Herein lies the premise of the treatise pursuant of creating an understanding of how patients can manage their lifestyle to embrace and/or mitigate cognitive decline.

Insulin resistance

Due to the high metabolic demand for energy in the brain, small perturbations in glucose metabolism can noticeably impact cognitive performance. Diabetes has been linked with lower levels of neuronal growth factors[27], decreased brain volume[28] and higher incidence of all types of dementia[29]. In a study by Baker et al[30], it was shown that when a memorization task was assigned to test the recalling ability of diabetics and pre-diabetics against a control population, subjects with healthy glucose metabolism remembered more words and interestingly, Fludeoxyglucose-Positron Emission Tomography (FDG-PET) scans of those with pre-diabetes/diabetes resembled brain scans of AD patients. The paper of Alagiakirshnan et al[13] addressed the context of antidiabetic drugs and their potential role in treating mild cognitive impairment and AD and concluded that "while it remains unclear whether management of diabetes will reduce the incidence of mild cognitive impairment (MCI) and AD, emerging evidence suggests that diabetes therapies may improve cognitive function". As evident from the forgoing discussions, the incidence of both diabetes mellitus and dementia increases with aging and the incidence of dementia are higher in people with diabetes. Although diabetes mellitus seems to be an independent risk factor for MCI and AD, evidence is pointing to the potential that insulin affects central nervous system functions and hence can modulate cognitive functions. Impaired insulin signaling and insulin resistance in the brain may play an important role in the pathogenesis of AD[31]. The exact mechanism by which insulin improves cognitive function is unknown but molecular interactions between insulin signaling, amyloid beta (a protein involved in the formation of senile plaques that can lead to AD) and tau phosphorylation are widely reported. It has been shown that amyloid can inhibit insulin signaling. Amyloid beta expression decreases AKT phosphorylation and disrupts insulin signal transmission, likely by inhibiting the interaction between AKT and PDK1, and amyloid beta can also directly compete with insulin to decrease its binding to insulin receptors. The interplay between insulin signaling, amyloid beta, and tau phosphorylation will likely contribute to any long-term benefits of insulin[31].

Inflammation

The inflammatory process in the brain is unique in that the blood-brain barrier (tight layer of endothelial cells that separates the brain from regular systemic circulation), during healthy conditions, prevents the infiltration of inflammatory agents and allows only select nutrients and small molecules into the central nervous system (CNS)[32]. However, chronic systemic inflammation induced by stimuli such as cigarette smoking, obesity,

disrupted sleep patterns and poor dietary habits compromises the integrity of the blood-brain barrier, allowing irritants to enter the brain and stimulate the production of inflammatory cytokines, such as IL-1β, IL-6 and IL-18. Inside the CNS, these cytokines impair neurogenesis, the process by which new neurons are generated[33,34]. Aside from inhibiting neurogenesis, some inflammatory cytokines, such as IL-1β, IL-6 and TNF-α damage and destroy existing neurons[35]. Yaffe et al[36] assessed the potential contribution of metabolic syndrome as a risk factor for cognitive decline and if this can be modified by inflammation. This important study sought to establish if biomarkers of inflammation could be linked with cognitive impairment. The 5-year prospective observational study looked at the association of the metabolic syndrome and high inflammation (defined as above median serum level of interleukin 6 and C-reactive protein) with changes in cognition. Metabolic syndrome may contribute to cognitive impairment in elders, but primarily in those with high level of inflammation. Indeed, serum markers of inflammation, especially IL-6 and CRP, are prospectively associated with cognitive decline in well-functioning elders[36]. This contributes to defining that inflammation contributes to cognitive decline in the elderly.

Oxidative Stress

The brain is particularly prone to free radical attacks owing to its relatively low antioxidant content, a considerable amount of polyunsaturated fatty acid chains in the neuronal membrane lipids and its high oxygen consumption rate[37]. The pathological hallmarks of AD include high levels of oxidative stress (defined by the status when endogenous antioxidant protection is overwhelmed by increased level of oxidants), intra-neuronal amyloid beta peptide accumulation, extracellular senile amyloid plaques, intraneuronal and extraneuronal neurofibrillary tangles made of hyper-phosphorylated tau, loss of synapses, loss of neurons and neuritic degeneration and gliosis. This pathology culminates in clinical signs predominantly associated with impaired cognitive processes. The underlying cause and molecular inter-relationship between these pathological entities and a full understanding of the cell signaling pathways relevant to neuronal death/survival is critical for informed discovery of compounds to combat AD. One of the major role of the mitochondria in brain metabolism is the provision of ATP via oxidative phosphorylation in order to drive energy-dependent processes[38] (**Figure 1**). Amyloid-β (A-beta) increases the level of mitochondrial reactive oxygen species (ROS) production. The sources of ROS-mediated damage appear to be multi-faceted in AD, with interactions between abnormal mitochondria, redox transition metals, and other factors. Amyloid precursor protein (APP) is found in mitochondria and may accumulate exclusively in the protein import channels of mitochondria of human AD brains but not in age-matched controls. The levels of translocationally arrested mitochondrial APP directly correlate with mitochondrial dysfunction and severity of the disease. Neuropathologic findings of β-amyloid plaques and intraneuronal neurofibrillary tangles remain the gold standard for diagnosis of Alzheimer's disease. The association of the APOE e4 allele with AD is significant; however, APOE genotyping is neither fully specific nor sensitive. While APOE genotyping may have an adjunct role in the diagnosis of AD in symptomatic individuals, it may have little role at this time in predictive testing of asymptomatic individuals[39]. Aruoma et al[40] investigated the potential cytotoxic effect of aggregated A-beta (1-42) to neurons that express several classical neurotransmitters (such as acetylcholine, catecholamines, serotonin and gamma-amino butyric acid. Aggregated A-beta (1-42) has a multisystem cytotoxic effect causing non-specific reduction in

immunoreactivity, dysfunction or loss of retinal nerve cells. Using immunocytochemistry, TUNEL staining for apoptosis and measurement of cell density as well as retinal surface area, a differential acute and/or chronic effect of A-beta on choline acetyl transferase, gamma-aminobutyric acid and 5-tryptamine hydroxylase systems, was observed with the increasing time course of 6h to 5 months and a bilateral/systemic effect. In contrast, the overall pattern of catecholaminergic system, as revealed by tyrosine hydroxylase immunoreactivity of the retina, appears to have remained relatively unaffected by A-beta (however this may reflect neuronal loss due to reduction in the retinal surface). This *in vivo* evidence in a CNS model shows that not only all major neurotransmitter systems are differentially affected by A-beta aggregates, but the effect may vary from one transmitter system to another under the same experimental conditions *in situ* and in a dose- and time-dependent manner[40].

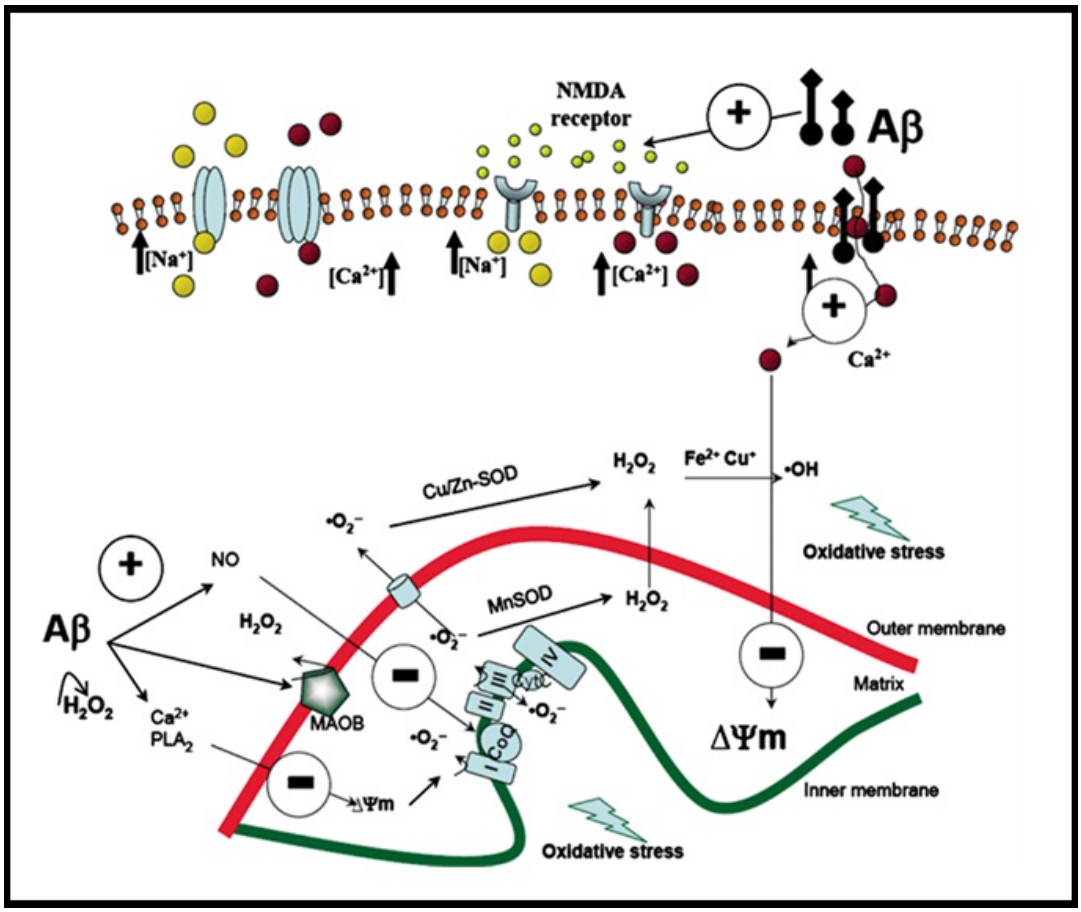

Figure 1. Mitochondrial biology in Alzheimer's disease pathogenesis depicting the potential role of Amyloid-β (Aβ). Mitochondria play a critical role in brain metabolism, their major role being the provision of ATP via oxidative phosphorylation to drive energy-dependent processes. Loss of complex IV activity represents key cytopathologies in Alzheimer's disease. Oxidative damage contributes to Alzheimer's disease pathogenesis. Amyloid-β increases mitochondrial reactive oxygen species (ROS) production. The sources of ROS-mediated damage appear to be multi-faceted in Alzheimer's disease, with interactions between abnormal mitochondria, redox transition metals, and other factors. Through mitochondrial electron transport chain, a proton motive force is generated as a result of a pH gradient and a transmembrane electrical potential (ΔΨ). ATP is synthesized when protons flow back to the mitochondrial matrix. Hypo-metabolism has long been implicated in the onset of both familial and sporadic forms of AD. (*From: Galindo FF, Ikuta I, Zhu X, Casadesus G, Jordán J. Mitochondrial biology in Alzheimer's disease pathogenesis. Journal of Neurochemistry. 2010; 114: 933–945. Copy right permission from John Wiley & Sons Inc*.)

Hormonal Imbalance

Distributed throughout the brain are steroid hormone receptors which function to regulate the transcription of a vast array of genes involved in cognition and behaviour[41]. Cognitive performance among older people is complex and dependent on many factors and in spite of the known effects of clinical thyroid disorders on cognitive function, little is known about the relationship between thyroid hormone (TH) levels and cognitive performance among older people with levels of TH within the normal reference range. Since thyroid hormone concentrations change with age and since cognitive decline is often concomitant with aging, physiological changes in thyroid function might be causally related to changes in cognition during normal aging[42]. When hormonal imbalances or deficiencies disrupt receptor activation, cognitive deficits and emotional turmoil are the results. Feinkohl et al[43] in the Edinburgh Type 2 Diabetes Study conducted a cross-sectional analysis of 1066 men and women aged 60-75 with Type 2 Diabetes during which they found that raised plasma NT-proBNP was weakly but statistically significantly associated with poorer cognitive function and depression. A further viewpoint on the hormonal contribution to cognitive function can be derived from the work of Wijsman et al[44]. Subclinical thyroid dysfunction has been implicated as a risk factor for cognitive decline in old age, but results are inconsistent. A prospective longitudinal study of men and women aged 70-82 years with pre-existing vascular disease or more than one risk factor to develop vascular disease concluded that there was no consistent association of subclinical hyper- or hypo-thyroidism with altered cognitive performance compared to euthyroid participants on the individual cognitive tests. Although there was no association with rate of cognitive decline during follow-up, the consensus of opinion was that a large randomized controlled trial can provide definitive evidence for the clinical and subclinical hypothyroidism as well as overt hyperthyroidism in middle-aged and elderly adults thought to be associated with decreased cognitive functioning as memory, reaction time, and visuo-spatial organization. While this type of study may also confirm or reject the notion of causality between TSH abnormalities and dementia[43,44], the potential of the disruption of the cerebral white matter network being associated with the slowing of information processing speed in patients with Type 2 Diabetes is widely debated[45]. Reijmer et al[46], have shown that patients with Type 2 Diabetes have alterations in local and global network properties compared with controls. These structural network abnormalities were related to slowing of information processing speed in patients, which may be independent of cerebrovascular lesion load. Thus, characterizing the brain as a network using Diffusion Magnetic Resonance Imaging and graph theory can provide new insights into how abnormalities in the white matter affect cognitive function in patients with Diabetes.

INSULIN AND ITS EFFECTS ON THE BRAIN

Insulin plays a role in brain physiology and disturbances of cerebral insulin signaling and glucose homeostasis are implicated in brain pathology[47]. When insulin's signal is ignored by cells, the brain may not get the large amount of glucose energy it needs, especially for memory. As a result, loss of brain cells affects cognitive functioning. Increased insulin concentrations also appear to boost levels of beta-amyloid. Insulin and related growth proteins in the brain are vital for cell survival and both glucose and insulin appear to regulate many brain functions, including learning and memory[4]. Dysfunction of these chemicals contributes to cognitive deficits. Chronic episodes of high or low levels of blood glucose may directly affect insulin's actions in the brain or damage

brain cells, leading to cognitive impairments. Diabetes mellitus is associated with cognitive deficits, which are paralleled by neurophysiological and structural changes in the brain. MRI scans are often performed to determine structural changes at the level of the brain. Brain cells have on their surface, their own insulin-receptors. In a study, Kahn et al[48] found that reduction in expression of major transcriptional regulator of cholesterol metabolism, SREBP-2 and its downstream genes in the hypothalamus and other areas of the brain, lead to reduction in brain cholesterol synthesis and synaptosomal cholesterol content. These changes are, at least in part, due to direct effects of insulin to regulate these genes in neurons and glial cells and can be corrected by intracerebroventricular injections of insulin.

Cognitive functioning can be measured in terms of intelligence, memory, language, executive function and visual function and assessment of these neuropsychological processes can help to diagnose for cognitive deficits. Each of these functions is controlled by specific domains of the brain. Diabetes affects the hippocampus, which is involved in learning and memory. In animal models of diabetes, impairments of spatial learning occur in association with distinct changes in hippocampal synaptic plasticity. At the molecular level, these impairments might involve changes in glutamate-receptor subtypes, in second-messenger systems and in protein kinases. The pathogenesis can be divided into three main components: (1) direct 'neurotoxic' effects of hyperglycemia, including increased polyol pathway flux, oxidative stress, enhanced formation of advanced glycated end-products and disturbances of Ca2+ homeostasis; (2) vascular changes, including alterations in cerebral blood flow and angiopathy; (3) alterations in neurotrophic support and neuromodulatory changes related to alterations in insulin and its receptors in the brain. It is important to note that the toxic effects of hyperglycemia might also affect the vasculature, thus compromising cerebral blood flow. Treatment with insulin might therefore not only correct hyperglycemia, but could also directly affect the brain[49]. The hypothalamus (a brain region that regulates metabolic processes and activities like hunger, thirst and body temperature) also appears to be involved, especially areas that respond to low blood sugar and regulate energy balance, body weight and the sensitivity of the liver and muscles to insulin. Verbal memory also appears to be impaired in groups with Type 2 Diabetes when compared with non-diabetic controls. Other cognitive domains, including visuo-spatial memory, attention and concentration and frontal lobe/ executive function, have tended to be less consistently affected[50].

MEASUREMENT OF COGNITIVE IMPAIRMENT

Cognition, commonly known as 'process of thought', refers to an information processing view of an individual's psychological functions, which include processes such as memory, language, perception and problem solving[51,52]. Cognitive testing is a way of assessing the cognitive capabilities of an individual and thus serves as a tool for determining neurological problems. Winblad et al[53] stated that no standardized assessment exists for the early stages of mild cognitive impairment which arise from diabetes. The need for repeated cognitive testing for those with diabetes should become a standard part of the evaluation and treatment part of diabetes, but the question remains which tests to use. There exists a battery of cognitive tests designed to assess different areas of cognition. Some commonly used tests are Trail Making Tests (Part A and Part B), Mini Mental Status Examination, Mini-Cog Test, General Practitioner's assessment of Cognition, Digit Symbol Test, Word List Fluency and Word List Memory and

Montreal Cognitive Assessment. These tests assess the domains of attention and concentration, executive functions, memory, language, visuo-constructional skills, conceptual thinking, calculations and orientation. The other biomarkers that are relevant in diagnosing neurodegenerative diseases related to diabetes include but not limited to: (1) Biomarkers of glucose metabolism: Glycated Hemoglobin (HbA1c) and Fasting Blood Glucose; (2) Biomarkers of Inflammation: Pro-inflammatory cytokines like Interleukin-1, Interleukin-6, Tumor Necrosis Factor Alpha and acute phase proteins like C-reactive protein and alpha-antichymotrypsin and as well as homocysteine; (3) Biomarkers of Oxidative stress: Isoprostane; (4) Biomarkers of lipoprotein metabolism: Apolipoprotein E, Total cholesterol, HDL, LDL, Triglycerides; and (5) Erythrocyte 2,3-diphosphoglycerate, Ferritin, Uric acid, Alanine Aminotransferase and Aspartate Aminotransferase.

DRUG THERAPY AND FUNCTIONAL FOODS/SUPPLEMENTS MODALITY IN THE MANAGEMENT OF COGNITIVE IMPAIRMENT IN DIABETES

The work of Wahlqvist et al[54] is indeed of interest as they showed that the combination of sulfonylurea and metformin (but not either one alone) significantly reduced both the incidence and relative risk for affective disorder in association with Type 2 Diabetes, irrespective of gender. The finding that the incidence of affective disorder was lower for patients with Type 2 Diabetes taking sulfonylurea and metformin than it was for their peers who were not taking these agents is "not entirely unexpected,"[55] and it has been pointed out that pioglitazone (antihyperglycemic drug) also has antidepressant properties.

Berr et al[56], found that that people with low cognitive functioning had higher probability of having low carotenoid levels which may suggest a preventive role for carotenoids in cognitive impairment. The antioxidant properties of plant/herbal extracts are attributed to the presence of phenolic compounds, which are mostly derivatives, and/or isomers of flavones, isoflavones, flavonols, catechins, tocopherols and phenolic acids. These bioactive components are potentially accessible to consumers through diet and the multifunctional nature of these components (in particular flavonoids) makes them ideal candidates for further investigations into the possible beneficial effects in neurodegenerative diseases[57]. In order to establish neuroprotective properties of antioxidants, it is crucial to measure 'markers' of oxidative damage (including neuronal loss) in the central nervous system and examine how they are affected by plant/herbal extracts and dietary antioxidants. So, can functional dietary supplements help in the management of diabetes and also reduce the risks for cardiovascular disease, neurological disease and other conditions worsened by inflammation and oxidative stress, including cognitive decline and depression? The question that needs to be fully addressed is can nutritional antioxidants/nutraceuticals and/or dietary supplements enable maintenance of integrity in the face of decreasing cognition associated with diseases of overt inflammation/neuroinflammation and age associated diseases.

CONCLUSION

The prevalence of diabetes in the elderly is growing as a result of both the increase of life expectancy and incidence of diabetes in the general population. It is understandable that the consequences of diabetes can exacerbate degenerative complications and the effects of co-morbidities. The use of available therapeutic drugs coupled with nutraceutical adjuncts could represent a potential therapeutic strategy for the reduction of mental-health consequences and serve as a preventive measure for at-risk individuals. An understanding of the mechanisms of diabetes-related cognitive

impairment and the resulting behaviors of patients can help healthcare professionals implement treatments to significantly improve health status and quality of life of patients with diabetes.

Author affiliations
[1]Department of Pharmaceutical Sciences, School of Pharmacy, American University of Health Sciences, Signal Hill, CA 90755, USA
[2]ANDI Center for Biomedical and Biomaterials Research, University of Mauritius, MSIRI Building, Réduit, Republic of Mauritius
[3]Touro College of Health Sciences, Bay Shore, New York, NY 11706, USA
[4]Groupe d'Etude sur l'Inflammation Chronique et l'Obésité (GEICO), Université de La Réunion, Saint Denis, Plateforme CYROI, France
[5]Apollo Bramwell Hospital, Moka, Mauritius

REFERENCES

1. American Diabetes Association. Standards of medical care in diabetes--2012. *Diabetes Care*. 2012;35 Suppl 1:S11-63.
2. Aruoma OI, Neergheen VS, Bahorun T, Jen LS. Free radicals, antioxidants and diabetes: Embryopathy, retinopathy, neuropathy, nephropathy and cardiovascular complications. *Neuroembryol Aging*. 2007;4(3):117-37.
3. Camera A, Hopps E, Caimi G. Diabetic microangiopathy: physiopathological, clinical and therapeutic aspects. *Minerva Endocrinol*. 2007;32(3):209-29.
4. Crane PK, Walker R, Hubbard RA, Li G, Nathan DM, Zheng H, et al. Glucose levels and risk of dementia. *N Engl J Med*. 2013; 369(6):540-8.
5. Abbatecola AM, Rizzo MR, Barbieri M, Grella R, Arciello A, Laieta MT, et al. Postprandial plasma glucose excursions and cognitive functioning in aged type 2 diabetics. *Neurology*. 2006;67(2):235-40.
6. Walther K, Birdsill AC, Glisky EL, Ryan L. Structural brain differences and cognitive functioning related to body mass index in older females. *Hum Brain Mapp*. 2010;31(7):1052-64.
7. Feil DG, Zhu CW, Sultzer DL. The relationship between cognitive impairment and diabetes self-management in a population-based community sample of older adults with type 2 diabetes. *J Behav Med*. 2012;35(2):190-9.
8. Gonzalez JS, McCarl LA, Wexler DD, Cagliero E, Delahanty L, Soper TD, et al. Cognitive Behavioral Therapy for Adherence and Depression (CBT-AD) in Type 2 Diabetes. *J Cogn Psychother*. 2010; 24(4):329-43.
9. Tuomilehto J, Lindström J, Eriksson JG, Valle TT, Hämäläinen H, Ilanne-Parikka P, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med*. 2001;344(18):1343-50.
10. Aruoma OI, Hayashi Y, Marotta F, Mantello P, Rachmilewitz E, Montagnier L. Applications and bioefficacy of the functional food supplement fermented papaya preparation. *Toxicology*. 2010; 278(1):6-16.
11. Somanah J, Aruoma OI, Gunness TK, Kowelssur S, Dambala V, Murad F, et al. Effects of a short term supplementation of a fermented papaya preparation on biomarkers of diabetes mellitus in a randomized Mauritian population. *Prev Med*. 2012;54:S90-7.
12. Bahorun T, Luximon-Ramma A, Neergheen-Bhujun VS, Gunness TK, Googoolye K, Auger C, et al. The effect of black tea on risk factors of cardiovascular disease in a normal population. *Prev Med*. 2012;54:S98-102.
13. Alagiakrishnan K, Sankaralingam S, Ghosh M, Mereu L, Senior P. Antidiabetic drugs and their potential role in treating mild cognitive impairment and Alzheimer's disease. *Discov Med*. 2013;16(90):277-86
14. Perrin BM, Swerissen H, Payne CB, Skinner TC. Cognitive representations of peripheral neuropathy and self-reported foot-care behaviour of people at high risk of diabetes-related foot complications. *Diabet Med*. 2014;31(1):102-6.
15. Le Floch JP, Doucet J, Bauduceau B, Verny C; SFD/SFGG Intergroup. Retinopathy, nephropathy, peripheral neuropathy and geriatric scale scores in elderly people with Type 2 Diabetes. *Diabet Med*. 2014;31(1):107–11.
16. Broadhurst CL, Polansky MM, Anderson RA. Insulin-like biological activity of culinary and medicinal plant aqueous extracts in vitro. *J Agric Food Chem*. 2000;48(3):849-52.
17. Qin B, Nagasaki M, Ren M, Bajotto G, Oshida Y, Sato Y. Cinnamon extract prevents the insulin resistance induced by

a high-fructose diet. *Horm Metab Res*. 2004;36(2):119-25.
18. Khan A, Safdar M, Ali Khan MM, Khattak KN, Anderson RA. Cinnamon improves glucose and lipids of people with type 2 diabetes. *Diabetes Care*. 2003;26(12): 3215-8.
19. Anisimov VN, Berstein LM, Egormin PA, Piskunova TS, Popovich IG, Zabezhinski MA, et al. Metformin slows down aging and extends life span of female SHR mice. *Cell Cycle*. 2008;7(17): 2769-73.
20. Onken B, Driscoll M. Metformin induces a dietary restriction-like state and the oxidative stress response to extend C. elegans Healthspan via AMPK, LKB1, and SKN-1. *PLoS One*. 2010;5(1):e8758.
21. Biessels GJ, Deary IJ, Ryan CM. Cognition and diabetes: a lifespan perspective. *Lancet Neurol*. 2008;7(2):184-90.
22. Cukierman T, Gerstein HC, Williamson JD. Cognitive decline and dementia in diabetes--systematic overview of prospective observational studies. *Diabetologia*. 2005;48(12):2460-9.
23. Ali S, Stone MA, Peters JL, Davies MJ, Khunti K. The prevalence of co-morbid depression in adults with Type 2 diabetes: a systematic review and meta-analysis. *Diabet Med*. 2006;23(11): 1165-73.
24. Craft S, Watson GS. Insulin and neurodegenerative disease: shared and specific mechanisms. *Lancet Neurol*. 2004;3(3):169-78.
25. Feldman H, Gracon S. Alzheimer's disease: symptomatic drugs under development. Gauthier S, ed. Clinical Diagnosis and Management of Alzheimer's disease. 1996:239-59.
26. Riddle AR. Brain Aging. Models, Methods, and Mechanisms, Frontiers in Neuroscience. Boca Raton (FL): CRC Press. 2007.
27. Pedersen BK, Pedersen M, Krabbe KS, Bruunsgaard H, Matthews VB, Febbraio MA. Role of exercise-induced brain-derived neurotrophic factor production in the regulation of energy homeostasis in mammals. *Exp Physiol*. 2009;94(12):1153-60.
28. McIntyre RS, Kenna HA, Nguyen HT, Law CW, Sultan F, Woldeyohannes HO, et al. Brain volume abnormalities and neurocognitive deficits in diabetes mellitus: points of pathophysiological commonality with mood disorders? *Adv Ther*. 2010;27(2):63-80.
29. Biessels GJ, Staekenborg S, Brunner E, Brayne C, Scheltens P. Risk of dementia in diabetes mellitus: a systematic review. *Lancet Neurol*. 2006;5(1):64-74.
30. Baker LD, Cross DJ, Minoshima S, Belongia D, Watson GS, Craft S. Insulin resistance and Alzheimer-like reductions in regional cerebral glucose metabolism for cognitively normal adults with prediabetes or early type 2 diabetes. *Arch Neurol*. 2011;68(1):51-7.
31. Morris JK, Burns JM. Insulin: an emerging treatment for Alzheimer's disease dementia? *Curr Neurol Neurosci Rep*. 2012;12(5):520-7.
32. Hickey WF. Leukocyte traffic in the central nervous system: the participants and their roles. *Semin Immunol*. 1999;11(2):125-37.
33. Peng H, Whitney N, Wu Y, Tian C, Dou H, Zhou Y, et al. HIV-1-infected and/or immune-activated macrophage-secreted TNF-alpha affects human fetal cortical neural progenitor cell proliferation and differentiation. *Glia*. 2013;56(8):903-16.
34. Liu YP, Lin HI, Tzeng SF.. Tumor necrosis factor-alpha and interleukin-18 modulate neuronal cell fate in embryonic neural progenitor culture. *Brain Res*. 2005;1054(2):152-8.
35. Marx CE, Jarskog LF, Lauder JM, Lieberman JA, Gilmore JH. Cytokine effects on cortical neuron MAP-2 immunoreactivity: implications for schizophrenia. *Biol Psychiatry*. 2001;50(10):743-9.
36. Yaffe K, Kanaya A, Lindquist K, Simonsick EM, Harris T, Shorr RI, et al. The metabolic syndrome, inflammation, and risk of cognitive decline. *JAMA*. 2004;292(18):2237-42.
37. Coyle JT, Puttfarcken P. Oxidative stress, glutamate, and neurodegenerative disorders. *Science*. 1993;262(5134):689-95.
38. Galindo FF, Ikuta I, Zhu X, Casadesus G, Jordán J. Mitochondrial biology in Alzheimer's disease pathogenesis. *J Neurochem*. 2010;114(4):933-45.
39. Mayeux R, Saunders AM, Shea S, Mirra S, Evans D, Roses AD, et al. Utility of the apolipoprotein E genotype in the diagnosis of Alzheimer's disease. Alzheimer's Disease Centers Consortium

on Apolipoprotein E and Alzheimer's Disease. *N Engl J Med*. 1998;338(8):506-11.
40. Aruoma OI, Jen SS, Watts HR, George J, Gentleman SM, Anderson PJ, et al. Acute and chronic effects of intravitreally injected beta-amyloid on the neurotransmitter system in the retina. *Toxicology*. 2009;256(1-2):92-100.
41. Mani SK, Portillo W, Reyna A. Steroid hormone action in the brain: cross-talk between signaling pathways. *J Neuroendocrinol*. 2009;21(4):243-7.
42. Annerbo S, Lökk J. A Clinical Review of the Association of Thyroid Stimulating Hormone and Cognitive Impairment. *ISRN Endocrinol*. 2013;2013: 856017.
43. Feinkohl I, Sattar N, Welsh P, Reynolds RM, Deary IJ, Strachan MW, et al. Association of N-terminal pro-brain natriuretic peptide with cognitive function and depression in elderly people with type 2 diabetes. *PLoS One*. 2012; 7(9):e44569.
44. Wijsman LW, de Craen AJ, Trompet S, Gussekloo J, Stott DJ, Rodondi N, et al. Subclinical thyroid dysfunction and cognitive decline in old age. *PLoS One*. 2013;8(3):e59199.
45. González HM, Tarraf W, Whitfield K, Gallo JJ. Vascular depression prevalence and epidemiology in the United States. *J Psychiatr Res*. 2012;46(4):456-61.
46. Reijmer YD, Leemans A, Brundel M, Kappelle LJ, Biessels GJ; Utrecht Vascular Cognitive Impairment Study Group. Disruption of the cerebral white matter network is related to slowing of information processing speed in patients with type 2 diabetes. *Diabetes*. 2013;62(6):2112-5.
47. Biessels GJ, Bravenboer B, Gispen WH. Glucose, insulin and the brain: modulation of cognition and synaptic plasticity in health and disease: a preface. *Eur J Pharmacol*. 2004;490(1-3):1-4.
48. Suzuki R, Lee K, Jing E, Biddinger SB, McDonald JG, Montine TJ, et al. Diabetes and insulin in regulation of brain cholesterol metabolism. *Cell Metab*. 2010;12(6):567-79.
49. Gispen WH, Biessels GT. Cognition and synaptic plasticity in diabetes mellitus. *Trends Neurosci*. 2000;23(11):542-9.
50. Frier BM. Hypoglycaemia and cognitive function in diabetes. *Int J Clin Pract Suppl*. 2001;123(123): 30-7.
51. Nasreddine ZS, Phillips NA, Bedirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc*. 2005; 53(4): 695-9.
52. Wong GK, Lam SW, Wong A, Ngai K, Poon WS, Mok V. Comparison of montreal cognitive assessment and mini-mental state examination in evaluating cognitive domain deficit following aneurysmal subarachnoid haemorrhage. *PLoS One*. 2013;8(4): e59946.
53. Winblad B, Palmer K, Kivipelto M, Jelic V, Fratiglioni L, Wahlund LO, et al. Mild cognitive impairment--beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. *J Intern Med*. 2004;256(3):240-6.
54. Wahlqvist ML, Lee MS, Hsu CC, Chuang SY, Lee JT, Tsai HN. Metformin-inclusive sulfonylurea therapy reduces the risk of Parkinson's disease occurring with Type 2 diabetes in a Taiwanese population cohort. *Parkinsonism Relat Disord*. 2012;18(6):753-8.
55. Berk M. Pathways to new drug discovery in neuropsychiatry. *BMC Med*. 2012;10:151.
56. Akbaraly NT, Faure H, Gourlet V, Favier F, Berr C. Plasma carotenoid levels and cognitive performance in an elderly population: results of the EVA Study. *J Gerontol A Biol Sci Med Sci*.. 2007;62(3):308-16.
57. Aruoma OI, Repine J, Coles S. Dietary nutraceuticals and age management medicine. *Prev Med*. 2012;54 Suppl:590-7.