Diabetes as a risk factor for neurodegenerative diseases

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Abbreviations

DM - Diabetes mellitus

NDD - Neurodegenerative diseases

AD - Alzheimer’s disease

PD - Parkinson’s disease

HD - Huntington’s disease

MCI - Mild cognitive impairment

T1DM - Type 1 Diabetes mellitus

T2DM - Type 2 Diabetes mellitus

AGEs - Advanced glycation end products

ROS - Reactive oxygen species

BBB - Blood brain barrier

CNS - Central nervous system

T3DM - Type 3 Diabetes mellitus

HbA1c - Glycated hemoglobin

APP - amyloid precursor protein

PSEN1 - presenilin1

PSEN2 - presenilin 2

RNS - Reactive nitrogen species

APOE - Apolipoprotein E

VEGF - Vascular Endothelial Growth Factor

WMH - White matter hyperintensity

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Summary

Title: Diabetes as a risk factor for neurodegenerative diseases

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Both diabetes mellitus and neurodegenerative diseases have become major health challenges worldwide. Diabetes mellitus is now known to be a major risk factor for cognitive decline, dementia and Parkinson's disease. It has also been shown that the risk of cognitive decline and neurodegeneration is not only seen in diabetic patients, but it is also increased in patients with prediabetes and metabolic syndrome. Chronic hyperglycemia suppresses substantia nigra dopaminergic neuronal firing and decreases dopamine turnover, as well as induces chronic brain insulin resistance, ultimately leading to impaired brain insulin signaling. Recent studies have focused on the role of insulin and impaired insulin signaling as a link between diabetes and neurodegenerative diseases. Impairments in brain insulin signaling mechanisms, together with hyperglycemia, might induce the molecular and biochemical changes such as dysfunction of the mitochondria, oxidative damage, and inflammatory responses, ultimately leading to pathological lesions seen in neurodegenerative diseases, as well as in diabetes mellitus. In addition, microvascular changes are also a critical factor involved in the etiology of diabetes mellitus and neurodegenerative diseases. Taken together, the complex systemic effects of diabetes mellitus on neurodegenerative diseases require further investigation.

Keywords: diabetes, neurodegenerative diseases, Alzheimer's, Parkinson's

Sažetak

Naslov: Dijabetes kao rizik za razvoj neurodegenerativnih bolesti

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Šećerna bolest i neurodegenerativne bolesti postale su velikim zdravstvenim izazovima današnjice. Šećerna bolest poznata je kao glavni faktor rizika za kognitivne poremećaje, demencije i Parkinsonovu bolest. Rizik za razvoj neurodegenerativnih bolesti i kognitivnih poremećaja nije samo povećan kod šećerne bolesti, već i kod pacijenata s predijabetesom ili metaboličkim sindromom. Kronična hiperglikemija potiskuje “paljenje” dopaminergičkih neurona substantije nigre i smanjuje omjer dopamina i njegovih metabolita, te inducira kroničnu inzulinsku rezistenciju u mozgu i dovodi do promijenjene signalizacije inzulina u mozgu. Nedavne studije usmjerene su na ulogu inzulina i promijenjenu signalizaciju inzulina kao poveznicu između dijabetesa i neurodegenerativnih bolesti. Oštećenja u mehanizmima signalizacije inzulina u mozgu, zajedno s hiperglikemijom, mogu izazvati molekularne i biokemijske promjene kao što su disfunkcija mitohondrija, oksidativni stres, i upalni odgovori, što u konačnici dovodi do patoloških lezija u neurodegenerativnim bolestima, kao i do šećerne bolesti. Osim navedenih promjena, mikrovaskularne promjene ključni su čimbenik u etiologiji šećerne bolesti i neurodegenerativnih bolesti. Stoga, s obzirom na vrlo kompleksnu pozadinu ovih procesa, složeni sistemski učinci šećerne bolesti na razvoj neurodegenerativnih bolesti zahtijevaju daljnje istraživanje.

Ključne riječi: šećerna bolest, neurodegenerativne bolesti, Alzheimer, Parkinson

1. Introduction

Diabetes mellitus (DM) is one of the fastest growing health challenges of the 21st century, with the number of adults living with it having more than tripled over the past 20 years (International Diabetes Federation, 2017), resulting in the global prevalence of DM in persons older than 18 years of 8,5% (World Health Organization, 2014). This prevalence rises to 12-15% in persons older than 65 years (Wild et al, 2004).

With the aging population, neurodegenerative diseases (NDD) have also become a major burden. Alzheimer's disease (AD) and Parkinson's disease (PD), the most common types of NDDs, affect more than 50 million people worldwide (Global burden of disease study, 2015). Out of more than a 100 neurodegenerative disorders known (McKusick et al, 2004), 20% are associated with DM (Ristow, 2004). Comparing this to the prevalence of DM of 8,5% in the general population, the prevalence of DM among persons suffering from NDDs is substantially higher, although there is not enough information on the exact, overall statistics.

The effects of DM on the brain are now well recognized. It is known to be a major risk factor for cognitive decline, dementia and PD (Verdile et al, 2015, De Pablo-Fernández et al, 2018). Many studies show that the risk of cognitive decline and neurodegeneration is also increased in patients with prediabetes and metabolic syndrome (Luchsinger et al, 2004). Most intriguing is the possibility that PD, AD and type II diabetes share common abnormal cellular processes in the brain. For example, new evidence demonstrates that insulin signaling may be abnormal in AD, PD and neurodegenerative diseases in general. In addition, dysfunction of the mitochondria (the cell's energy producing

center), oxidative damage, and inflammatory responses, may all play a role in diabetes as well as in neurodegenerative diseases (De Pablo-Fernández et al 2018, Barilar et al 2020). Etiology of diabetes and neurodegenerative diseases is quite complex, but based on literature data, we will try to summarize potential mechanisms underlying hypoglycemia/hyperglycemia-induced impairment of brain function.

2. Diabetes Mellitus

2.1. Definition and classification

Diabetes mellitus is a clinical syndrome characterized by inappropriate glucose metabolism resulting in hyperglycemia caused by relative or absolute deficiency of insulin, most commonly due to Type 1 (T1DM), or Type 2 Diabetes Mellitus (T2DM). Lack of insulin affects the metabolism of carbohydrates, proteins and fats, and can cause significant disturbance of water and electrolyte homeostasis.

DM is associated with an array of microvascular, macrovascular, and neuropathic complications, most commonly affecting the eye (retinopathy), the kidney (nephropathy), the cardiovascular system (coronary artery disease, cerebrovascular disease, peripheral artery disease) and the nervous system (neuropathy) (Davidson, 2010).

According to the World Health Organization (WHO), the vast majority of diabetic patients are classified into one of two main categories: type 1 diabetes mellitus, which is caused by an absolute or near absolute deficiency of insulin, or type 2 diabetes mellitus, which accounts for 90-95% of all cases of DM worldwide (Zheng et al, 2017) and is characterized by the presence of insulin resistance with an inadequate response of insulin secretion. In addition, diabetes during pregnancy is classified as gestational diabetes, and finally, there is a variety of rare and diverse types of diabetes, caused by infections, drugs, endocrinopathies, pancreatic destruction, and genetic defects. These unrelated forms of diabetes are classified as “Other Specific Types”.

2.2. Type 2 Diabetes Mellitus

Type 2 Diabetes Mellitus is a more complex condition than T1DM because there is a combination of resistance to the actions of insulin in the liver and muscle together with impaired pancreatic ß-cells, which leads to “relative” insulin deficiency. Insulin resistance comes first, which means that there is an elevated insulin secretion in order to maintain normal blood glucose levels. In the setting of insulin resistance, the liver inappropriately releases glucose into the blood. However, other potentially important mechanisms associated with type 2 diabetes and insulin resistance include increased breakdown of lipids within adipocytes, resistance to and lack of incretin, high glucagon levels in the blood, increased retention of salt and water by the kidneys, and inappropriate regulation of metabolism by the central nervous system. However, not all people with insulin resistance develop T2DM since an impairment of insulin secretion by pancreatic ß-cells is also required.

Unlike T1DM, T2DM is commonly associated with visceral obesity, hypertension and dyslipidemia - all of these conditions predispose to cardiovascular disease, which altogether, is referred to as “insulin resistance syndrome” or “metabolic syndrome”.

At the time of diagnosis, around half of ß-cell function has been lost, and it worsens with time, with a slow onset of “relative” insulin deficiency. In T2DM hyperglycemia develops slowly, over months, or even years and there is a rise in the renal threshold for glucose, so that the glycosuria is limited. Thus, patients are often asymptomatic and only present with a long history of fatigue. If they, however, do present with symptoms, the classic symptoms are polyuria, polydipsia, polyphagia and weight loss. T2DM is usually

diagnosed based upon plasma glucose criteria obtained during fasting or a 2-h plasma glucose value following an oral glucose tolerance test where fasting plasma glucose is ≥7.0 mmol/L after at least an 8-h fast, or 2-h plasma glucose ≥11.1mmol/L during an oral glucose tolerance test. More recently, hemoglobin A1C (HbA1c) values ≥6.5% have been added as a third option in the diagnosis of T2DM (Standards of Medical Care in Diabetes, 2014).

2.3. Complications of diabetes

Diabetes is associated with an array of both acute and chronic complications. Here, I will focus only on the chronic complications affecting the microcirculation and the brain. Microvascular complications are characterized by the basement membrane thickening, due to hyperglycemia, of the smallest vessels and those include diabetic retinopathy, nephropathy, neuropathy and neurodegeneration, whereas damage to the large blood vessels leads to macrovascular complications such as coronary artery disease, peripheral artery disease and cerebrovascular disease.

The main focus of this thesis is the effect of diabetes on the brain, and more specifically on cognition, memory and motor function.

Hyperglycemia appears to be related to abnormalities in cognitive and motor function in patients with both type 1 and type 2 diabetes. However, the mechanisms through which hyperglycemia might mediate this effect are less than clear.

In other organs, hyperglycemia alters function through a variety of mechanisms

including polyol pathway activation, increased formation of advanced glycation end-products (AGEs), diacylglycerol activation of protein kinase C, and increased glucose shunting in the hexosamine pathway (Brownlee, 2001). These same mechanisms may be operative in the brain and induce the changes in cognitive and motor function that have been detected in patients with diabetes (Kodl and Seaquist, 2008).

In a study performed by Nunley et al. there has been found a higher white matter hyperintensity (WMH) on MRI in patients suffering from DM compared with healthy individuals indicating the damage of small vessels in periventricular and subcortical areas (Nunley et al., 2015, Tamura and Araki 2015). Also, slower information processing speed progression of cognitive decline and functional disability is associated with white matter hyperintensities (Nunley et al., 2015,Wardlaw et al., 2013 Tamura and Araki 2015). Additionally it has been reported that markers of insulin resistance and WMH are related in patients with DM (Anan et al 2010, Tamura and Araki 2015). Furthermore the WMH commonly observed on brain imaging of patients with Parkinson's disease (PD) are associated with balance, gait impairment and cognition (Herman et al 2013, Bohnen et al 2010).

3. Neurodegenerative diseases

3.1. Definition

Neurodegenerative diseases are characterized by a progressive loss of structure and function of neurons. The main feature in neurodegenerative brain disorders are loss of neurons and as a consequence we can see degeneration of one part of the brain (e.g. hypothalamus or substantia nigra) and in the end, we see the atrophy of the whole brain. Also, in neurodegenerative disorders, the deposition of proteins showing altered physicochemical properties in the brain and in the peripheral organs (also known as misfolded proteins) can be seen (Kovacs, 2017).

This heterogeneous group of chronic illnesses includes Alzheimer's disease, Parkinson's disease, motor neuron disease, the trinucleotide repeat disease (i.e. the autosomal dominant spinocerebellar ataxias and Huntington's disease (HD)), and many others. However, I will briefly describe the most common neurodegenerative disorders.

3.2. Alzheimer's disease

Alzheimer's disease is the most common cause of dementia, accounting for 60-70% of all cases. AD affects approximately 15% of individuals of age 65 years or older and approximately 45% of those aged 85 or more (Aminoff et al, 2015). Its prevalence is estimated to be more than 45 million cases worldwide (Global burden of disease study, 2015).

AD is a progressive, neurodegenerative disorder that is usually divided into late onset sporadic AD (95% of all AD cases) and rare early onset familial form that accounts for 5% of all cases. The familial form is due to mutations in three major genes (amyloid precursor protein (APP) gene, presenilin1 (PSEN1) gene and presenilin 2 (PSEN2) gene) (Piaceri et al, 2013).

On the other hand the etiopathology of sporadic AD is complex and not yet elucidated. People with one ε4 allele have 3-4 times more chance to develop AD than those who do not have it and the risk of developing AD linked to apolipoprotein E (APOE) ε4 allele is two times greater in diabetic ε4 carriers (Sims-Robinson et al., 2010, Peila et al., 2002) AD is defined by characteristic histopathologic features, especially neuritic (senile) plaques - extracellular deposits mainly containing ß-amyloid but also other proteins, like APOE and synuclein. Plaques can also be found in the walls of cerebral and meningeal blood vessels, producing cerebral amyloid angiopathy. Another distinct histopathologic feature of AD are neurofibrillary tangles - intracellular deposits containing hyperphosphorylated tau protein and ubiquitin (Weller and Budson 2018. Aminoff et al, 2015).

The clinical progression of AD is thought to have a presymptomatic phase of about 10-15 years, which is characterized by the glucose hypometabolism, loss of neurons, increased phosphorylation of tau protein and increased amyloid beta 1-42 in cerebrospinal fluid, followed by a symptomatic phase during which amyloid plaques and neurofibrillary tangle formation occurs accompanied by extensive neuronal loss which is, at the end of the disease, seen as brain atrophy and enlarged ventricles (Mathis et al., 2003, Aminoff et al, 2015).

Early in the course of the disease, a term mild cognitive impairment (MCI) is often used to describe cognitive decline in patients who are later diagnosed with AD. It usually presents with impairment of recent memory and may be noticed only by family members. As the time goes by, the patients can become disoriented to time and place, and develop aphasia, anomia and acalculia, which forces them to stop working (Weller and Budson 2018, Aminoff et al, 2015).

In the late stages, psychiatric symptoms ensue, such as psychosis with paranoia, hallucinations and delusions. Rare features in the late stages of the disease include incontinence, spasticity and myoclonus. In the terminal phase of the disease complications like eating problems, dyspnea, febrile episodes and pneumonia start to occur (Aminoff et al, 2015).

Currently available treatment options haven't shown to reverse symptoms or to stop the progression of the disease. However, some drugs such as memantine (an NMDA-type glutamate receptor antagonist) and acetylcholinesterase inhibitors may produce modest improvements (Weller and Budson 2018).

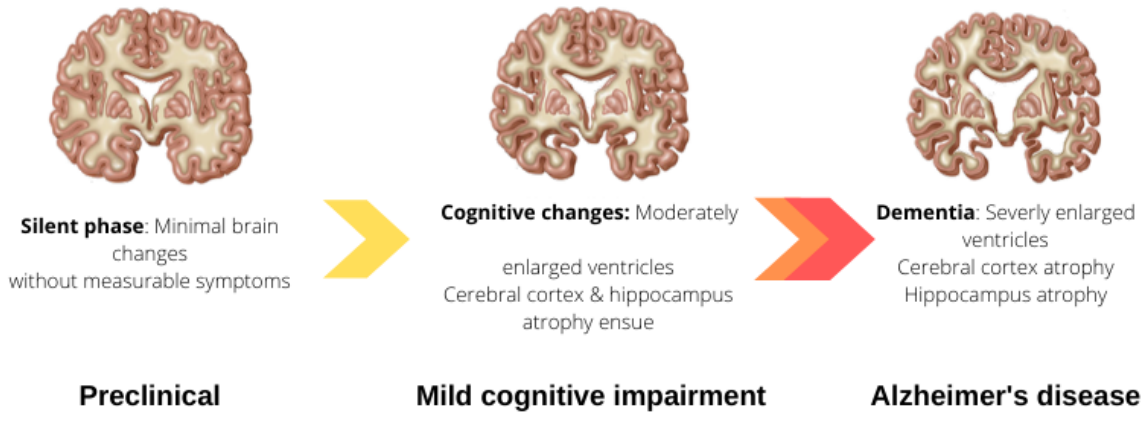

Figure 1: Progression of Alzheimer's disease

3.3. Parkinson’s disease

Parkinson’s disease (PD) is the second most common chronic neurodegenerative disorder, after Alzheimer’s disease. Currently, the cause(s) of the majority of PD cases remains unknown. Less than 10% of PD cases can be directly linked to monogenic mutations. Environmental factors, or a combination of both environment and genetic susceptibility, have been proposed to play a role in sporadic PD (Dauer and Przedborski, 2003). PD is diagnosed at advanced stages when more than 80% of dopaminergic neurons in substantia nigra is lost (Dauer and Przedborski, 2003) . Histopathologic findings present with loss of pigmentation and cells in the substantia nigra and other brainstem centers, cell loss in the globus pallidus and putamen, and Lewy bodies containing ⍺-synuclein in the basal ganglia, brain stem, spinal cord and sympathetic ganglia (Dauer and Przedborski, 2003).

The most prominent clinical findings are the motor abnormalities, including tremor, rigidity, hypokinesia and abnormal gait and posture, which appear to result from altered patterns of inhibition and excitation within the basal ganglia and its connection via direct and indirect pathways. Dopamine and acetylcholine act as neurotransmitters in this region, and in PD, the normal balance between these two antagonistic neurotransmitters is disturbed because of dopamine depletion in the dopaminergic nigrostriatal system (Aminoff et al, 2015).

PD also affects many other areas of the central nervous system, such as the dorsal motor nucleus of the vagus, the nucleus basalis of Meynert, the locus coeruleus, and the hypothalamus (Braak et al. 2004). Affection of those regions accounts for Non motor manifestations like cognitive decline, executive dysfunction and personality

changes, depression, anxiety and sleep disturbances (Chaudhuri et al, 2005). Furthermore, recent evidence suggests that non motor manifestation such as constipation, olfaction, rapid eye movement, behavior disorder, fatigue, and depression may be markers of a preclinical stage of PD (Chaudhuri et al, 2005) (Fig. 2). Currently there is no curative treatment for PD and all of the therapy is oriented towards symptoms relief. Treatment of the motor symptoms is directed towards enhancing dopaminergic transmission by levodopa, dopamine agonist and monoamine oxidase-B inhibitors, catechol-O-methyltransferase inhibitors. Also, clozapine is effective for hallucinations, cholinesterase inhibitors may improve symptoms of dementia and antidepressants and pramipexole may improve depression. As for the sporadic forms of AD and PD, the etiology is complex and the therapy is only symptomatic.

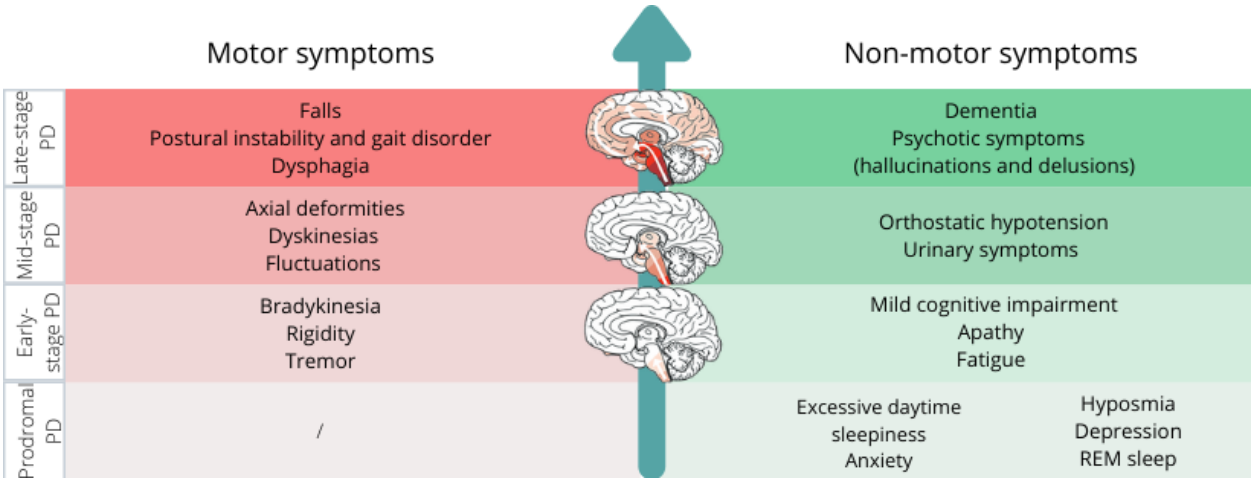

Figure 2: Progression of Parkinson's disease

4. Diabetes mellitus and the brain

4.1. Insulin resistance in the brain

Insulin was first isolated in 1922 by Banting and Best, and it is a major regulator of blood glucose levels, stimulating the uptake of glucose by the muscles, liver and adipose tissue. However, the uptake of glucose by the brain cells and its transport to the brain is almost entirely independent of insulin. The non-insulin sensitive glucose transporters GLUT-1 for blood brain barrier (BBB) and astrocytes, GLUT-3 for neurons and GLUT-5 for microglia are responsible for the majority of glucose uptake by the central nervous system (CNS) (McEwen and Reagan, 2004).

One would then assume that the CNS is an insulin-insensitive tissue, especially knowing that insulin, being a protein, shouldn't be crossing the BBB. Yet, there are many insulin receptors distributed throughout the brain, and insulin, in fact, is transported across the BBB using a saturable transport system (Schwartz et al., 1991; Baura et al., 1993; Poduslo et al., 1994; Banks et al., 1997). Some cells in the hypothalamus, hippocampus and cerebellum actually do possess the insulin-sensitive transporters such as GLUT-4 (Grillo et al, 2009) and GLUT-8, but it still doesn't change the fact that glucose uptake in the brain is largely independent of insulin. Therefore, insulin must have other functions in the brain.

One of the first actions found for insulin in the CNS is its effect on feeding and serum glucose. CNS insulin has opposite effects comparing to peripheral insulin - it increases blood glucose levels, decreases feeding and body weight and even decreases blood levels of insulin (Debons et al., 1970; Hatfield et al., 1974; Strubbe & Mein, 1977; Ajaya

& Haranath, 1982; Woods & Porte, 1983; Brief & Davis, 1984; Florant et al., 1991; Schwartz et al., 1992; Figlewicz et al., 1995; Bruning et al., 2000).

Even though peripheral increase in insulin and insulin resistance are known risk factors for the development of AD (Luchsinger et al., 2004), it seems that in the brain, it is the insulin deficiency that occurs in AD (Banks et al, 2012). There are many mechanisms explaining the connection between AD and insulin, one of them being the insulin's role as a growth factor in the CNS, affecting synaptogenesis and nerve growth (Nelson et al, 2008), meaning that insulin resistance could lead to cognitive decline (Hoyer, 2004). Furthermore, insulin has been suggested to have some other effects in the brain. For example, in rats, it has been found that down regulation of insulin receptor expression in hypothalamus results in depressive-like behavior (Grillo et al, 2011). Insulin receptors are distributed throughout the brain, especially in the olfactory bulb, cerebral cortex, hypothalamus, hippocampus and cerebellum (Havrankova et al, 1978;Unger et al., 1989; Wozniak et al., 1993). Insulin receptor levels are also higher in neurons than in glial cells (Unger et al., 1989) and these levels decrease with aging, suggesting its role in the aging process (Frolich et al., 1998; Chung et al., 2002; Bosco et al., 2011). Aging is also one of the biggest risk factors for PD, and normal aging is associated with a decrease in peripheral insulin receptor sensitivity. Studies indicate that mRNA levels of insulin receptors in the brain decline with age, particularly in the hypothalamus, cortex and hippocampus, and this leads to chronic secondary hyperinsulinemia (Kushner, 2013; Zhao et al., 2004). However, this physiological age-related decline in insulin signalling seems to be enhanced in PD. Studies show marked loss of insulin receptor mRNA in the substantia nigra pars compacta of patients with PD and increased insulin

resistance compared with age matched controls (Duarte et al., 2012; Morris et al., 2014; Takahashi et al., 1996). Furthermore, it has been shown that these changes may precede the death of dopaminergic neurons (Moroo et al., 1994).

Resistance to insulin at peripheral tissue receptors is called T2DM, and by extension, a resistance to insulin at the brain receptors is referred to as diabetes mellitus type 3 (T3DM). A few studies have reported resistance to insulin at the CNS receptors, showing less activation of cellular machinery when the cells are exposed to insulin (Banks et al., 2012).

William Banks and others have suggested that resistance to insulin at the peripheral receptors (T2DM) and at the CNS receptors (T3DM) may occur together, as well as independently (Banks et al., 2012). It remains unclear whether the effects of T2DM and T3DM on cognitive functions are similar and whether resistance to insulin in the CNS is an immediate result of insulin resistance at the peripheral tissues (Banks et al., 2012). However, it is clear that insulin action is very important for the health of the CNS and for the development of neurodegenerative diseases.

4.1.1. Effects of insulin, glycemic control and cognition

The term pre-diabetes is used when there is a presence of insulin resistance, although enough insulin is still produced to prevent a definite diabetes, but it results in impaired glucose tolerance and impaired fasting glucose levels (Luchsinger et al., 2004; Cole et al., 2007). In pre-diabetes, there is an abnormally high level of insulin, persisting for many years or even decades (Roriz-Filho et al., 2009). An excessively high level of insulin in the blood is correlated with neurodegeneration and cognitive decline

(Luchsinger et al., 2004), which was supported by studies evaluating neuropsychological performance in pre-diabetic individuals (Yaffe et al., 2004). Hyperinsulinemia and impaired glucose tolerance were correlated with reduced Mini Mental State of Examination scores (Folstein et al., 1975) and associated with an increased risk for mild cognitive impairment. In a study done by Convit and others, decreased glucose tolerance was linked with lower general cognitive performance, memory impairment and hippocampal atrophy on the MRI (Convit et al., 2003). Cognitive tests performed in people with high glycated hemoglobin compared to individuals having normal levels of HbA1c, showed decline in memory regardless of diabetes status (Zheng et al., 2018).

Impaired glucose tolerance is one of the components of metabolic syndrome, together with central obesity, hypertension, hyperlipidemia and hypercholesterolemia. Each of these is an individual risk factor for stroke, but when it comes to the pathogenesis of the peripheral or central neuropathy, hyperglycemia is more important than the other components (Singleton and Smith, 2006).

The detrimental effects of hyperglycemia on the brain are mediated through high levels of glucose activating the polyol and hexose pathways, inducing hyperosmotic stress in cells and generation of reactive oxygen species (ROS) and advanced glycation end products (AGEs) (Brownlee, 2001). ROS and AGEs are directly implied in aging, but all of these mentioned phenomena take part in inducing microvascular changes, leading to microinfarctions and brain atrophy and resulting in cognitive decline and dementia (White et al., 2002). There may also be an important relationship between neurodegeneration, insulin signalling and glucose utilisation in the brain. Using PET

imaging, Borghammer et al. have shown that patients with PD present with widespread cortical hypometabolism compared to control subjects, which is seen even in the early stage (Borghammer et al., 2010).

Similarly, abnormal cerebral glucose metabolism may also be linked to cognitive decline in PD. Significantly pronounced glucose hypometabolism in the frontal and parietal cortices is seen in PD patients with mild cognitive impairment and dementia, compared to controls of the same age (Hosokai et al., 2009; Huang et al., 2008; Liepelt et al., 2009; Yong et al., 2007) and may predict cognitive decline (Dunn et al., 2014; Peppard et al., 1992).

Also, studies have found that in healthy individuals peripheral insulin resistance is associated with cerebral glucose hypometabolism in the parietotemporal, frontal, and cingulate cortices (Baker et al., 2011) and that it may predict worse outcomes in memory (Willette et al., 2015b). Since PD has a diverse nature of pathophysiology underlying cognitive impairment, these patterns of cerebral regional hypometabolism are also seen in early stage AD, suggesting that insulin resistance may act as a predicting biomarker for identifying patients at risk of developing cognitive decline and AD (Baker et al., 2011; Willette et al., 2015a, 2015b)

Decreased cerebral glucose metabolism causes a rise in intracellular ATP/ADP, which, in turn, inactivates potassium channels - which modulate dopamine release from dopaminergic neurons (Levin, 2000), and increase the risk of cognitive decline (Willette et al., 2015b). Although this hypometabolism may not directly be related to insulin resistance in the neurons, as insulin does not directly affect neuronal glucose uptake, but this reduced cerebral glucose metabolism may occur as a secondary consequence

of reduced postsynaptic neurotransmission (resulting from reduced insulin signalling), as glutamate and other agents stimulate glucose uptake in the brain (Talbot and Wang, 2014).

4.2. Microvascular changes in Diabetes mellitus

Diabetes is associated with both functional and structural changes in the cerebral vascular system, which can, for example, increase the risk of neuronal damage and dysfunction in brain neurogenesis (Brands et al 2004). Microvascular changes affect the small arteries, arterioles, venules, and capillaries of the brain (Wardlaw et al., 2013). Early microvascular pathophysiological changes in DM comprise of the reduced availability of vasodilating molecules, in particular nitric oxide due to its binding to superoxide forming peroxynitrite, which plays a central role (Hosseini and Abdollahi, 2013). Additional vasoconstrictive factors, such as sympathetic tone and angiotensin II levels, are increased (Cameron et al 2001). Secondly, there are changes in endothelial function and neovascularization, which leads to blood–brain barrier hyperpermeability (Prakash et al., 2012; Horani and Mooradian, 2003). Thirdly, increased arterio-venous shunting reduces endoneurial blood flow (Cameron et al 2001). Later on, structural changes such as pericyte degeneration, capillary membrane thickening and decreased capillary density may occur in the brain (Johnson et al., 1982). All of the above mentioned changes have a significant impact on microvascular integrity in the brain of patients with T2DM. Furthermore, all of these changes in microvascular integrity can be seen on neuroimaging as recent small subcortical infarcts, lacunes, white matter

hyperintensities, perivascular spaces, microbleeds (Wardlaw et al., 2013, Imamine et al., 2011). The clinical manifestation can be presented as stroke or cognitive decline, or can be asymptomatic. As mentioned above, there are numerous studies reports on white matter hyperintensity in patients with T2DM, which is also related to impaired cognition in the patients with T2DM, (Manschot et al., 2006; Jongen et al., 2007; van Harten et al., 2007; Imamine et al., 2011) especially when it comes to processing speed, memory, attention and motor speed.

4.2.1. Endothelial dysfunction

As stated above, there are many pathways contributing to vascular changes leading to endothelial dysfunction. Dysfunctional endothelial cells have defective vasodilatory responses after agonist stimulation, and can not maintain barrier integrity leading to the formation of edema (Bonds et al., 2016). Loss of function of endothelial cells may contribute to the etiology of cardiovascular disease characterized by vascular hyperpermeability, chronic inflammation, and hypertension (Bonds et al., 2016). Therefore, disruption of the ability of the endothelial cells microenvironment to maintain homeostasis of partner cells may be linked to neuropathologies such as AD (Bonds et al., 2016).

The possible connection between functional changes in the vascular network and the viability of neural tissue impacting cognition, motion, and memory, as indicated in this study, is that inflammation affects the capacity of endothelium to transport peptides from the circulation to the surrounding tissues (Bonds et al., 2016). The endothelium is crucial in transporting a number of compounds through the blood vessel wall. Oxidative

stress accompanies inflammation and is significantly enhanced in diabetic patients (Brouwers et al., 2010; Giacco & Brownlee, 2010; Kohen Avramoglu et al., 2013; Pi et al., 2009; Stadler, 2012), providing a possible connection between chronic inflammation and changes in the endothelium that impact cerebrovascular homeostasis. It is, thus, very probable that reduced access of insulin to these areas would produce notable deficits in the ability of these cells to sustain themselves, function normally, and survive stress (Lazarov and Tesco, 2016).

4.2.2. Cerebral neovascularization dysfunction and neurogenesis

Several studies have shown that there is an increase in cerebral neovascularization in T2DM (Silvestre & Levy, 2006; Li et al., 2010; Prakash et al., 2013). However, these new, small vessels do not mature properly, resulting in an increase of non perfusable tissue and blood–brain barrier hyperpermeability (Prakash et al., 2012). Actually, this creates a hypoxic environment where the metabolic demands of the surrounding tissue cannot be met. However, it must be taken into account that these studies focused on neovascularization in the cerebral cortex and not on the neurogenic areas of the brain that are associated with learning and memory: the subgranular layer of the hippocampus and the subventricular zone.

Neurogenesis plays a role in the process of learning and memory (Zhao et al., 2008). Beauquis et al. showed that vascularization of the hippocampus is significantly decreased in T2DM (Beauquis et al., 2010). This same study also shows that, while there is a significant increase in the number of proliferating neuroblasts, these cells do

not survive to incorporate into the granular cell layer. Their findings propose that the survival of new neurons depends markedly on the brain's ability to provide functional vasculature. The formation of new neurons in both the subventricular zone and the subgranular layer are crucial to brain plasticity (Lazarov et al., 2010). This process of neurogenesis has been shown to be defective in AD (Demars et al., 2010; Lazarov et al., 2010) and this compromised vascular function observed in T2DM can also compromise the regenerative capacity of the brain, eventually causing and/or accelerating the onset of AD and PD.

4.4. Macrostructural brain changes in diabetes

As discussed before, many studies, using the conventional magnetic resonance imaging (MRI), have detected macrostructural brain changes occurring in the brains of diabetic patients (van Bussel et al., 2017).

In this subheading, I will briefly go through the recent evidence using brain imaging for cognitive impairment in T2DM, summarizing the studies investigating cognitive performance in patients with T2DM, using different MRI techniques.

4.4.1. Cerebral atrophy

Brain atrophy is defined as the shrinkage of brain tissue, which is a result of neuronal loss and its connection (Jobst et al., 1994). Many studies on T2DM, with the help of various MRI techniques, reported on brain atrophy (den Heijer et al., 2003; de Bresser et al., 2010; van Elderen et al., 2010). It has been found that there are associations

between brain atrophy and decreased cognitive performance in different aspects (Tiehuis et al., 2009; Hayashi et al., 2011; Moran et al., 2013; Zhang Y. et al., 2014), including memory, attention and higher executive function, speed of processing, motor and sensory speed.

4.4.2. Neuronal dysfunction

Neuronal dysfunction refers to a disorder in the central nervous system and it affects the brain processes, including reduced function in certain brain regions and connectivity between different brain regions (Zhou et al., 2010). Functional MRI has the ability to connect the increased neuronal activities to increased blood flow and oxygenation (van Bussel et al., 2017). Different studies, using a measure of spontaneous neuronal activity reported abnormal brain activity in diabetic patients (Zhou et al., 2010; Musen et al., 2012; Xia et al., 2013; Cui et al., 2014).

4.4.3. White matter tract abnormalities

White matter tract abnormalities refer to impaired integrity or altered organization of axonal bundles and can be studied using diffusion MRI. Diffusion MRI studies imply that patients with type 2 diabetes exhibit white matter tract, microstructure and network abnormalities (Yau et al., 2009; Falvey et al., 2013; Zhang J. et al., 2014, 2016; van Bussel et al., 2016b; Xiong et al., 2016).

Abnormalities in diffusion MRI were found in different tracts, including the superior longitudinal fasciculus (Reijmer et al., 2013), uncinate fasciculus (Reijmer et al., 2013; Hoogenboom et al., 2014), inferior longitudinal fasciculus (Reijmer et al., 2013), corpus

callosum (Reijmer et al., 2013), and cingulum bundle (Hoogenboom et al., 2014). These abnormalities were linked to defective processing speed and memory (Reijmer et al., 2013; Hoogenboom et al., 2014) and they point to an underlying glucose-mediated mechanism, as HbA1c hemoglobin and fasting blood glucose were also associated with these tract abnormalities (Hoogenboom et al., 2014). Moreover, altered hippocampal white matter connectivity appears to be associated with memory decline and type 2 diabetes (van Bussel et al., 2016b).

4.5. Common underlying processes in Alzheimer's, Parkinson's and Diabetes

Multiple studies have shown that diabetic patients have an increased risk of developing AD, compared with individuals who are not diabetic, but are of the same sex and age (Brands et al., 2005; Biessels et al., 2006). According to a study published in the journal *Diabetes*, more than 80% of AD cases presented with either T2DM or an impaired glucose metabolism disorder (data collected from the Mayo Clinic Alzheimer Disease Patient Registry) (Janson et al., 2004). In patients with T2DM, there was a significant positive correlation between the duration of diabetes and the density of Aβ plaques (Janson et al., 2004). Studies performed in diabetic animal models, which have been studied for AD pathology, discovered the presence of AD pathology in diabetes (Jash et al., 2019). Increase in tau phosphorylation was observed in post-mortem brains from patients with T2DM (Liu et al., 2009). There are several molecular connections which have been investigated to find a link between DM and AD. As mentioned above,

hyperglycemia can lead to many pathophysiological processes including ROS and AGEs formation causing damage to the brain (Biessels et al., 2002).

Besides its well-known role in AD, recent studies suggest that insulin resistance also occurs in the brains of patients with PD, probably as the contributing factor in the pathology of PD (Athauda and Foltynie, 2016). However, it was almost 60 years ago when scientists started to explore the possible connection between DM and PD. Studies showed that DM worsens both motor and cognitive deficits in patients with PD (Schwab, 1960), and that parkinsonian patients without DM present with glucose intolerance (Barbeau et al., 1961) and hyperglycemia (Boyd et al., 1971). Also, a diet rich in carbohydrates with high glycemic index has been associated with greater chances of developing PD (Cheng et al., 2009; Murakami et al., 2010; Yang and Cheng, 2010; Stafstrom and Rho, 2012).

Furthermore, both insulin resistance and downregulation of the insulin receptors in the substantia nigra have been found in PD patients (Moroo et al., 1994; Takahashi et al., 1996; Duarte et al., 2012). Possible mechanisms linking insulin resistance and PD might include ⍺-synuclein aggregation, inflammation in the neurons and defects in mitochondrial function (Athauda and Foltynie, 2016). Insulin signalling can affect the degradation of ⍺-synuclein and inhibit ⍺-synuclein fibril formation by activating the insulin-degrading enzyme (Sharma et al., 2015).

4.5.1. Oxidative stress and Inflammation

Hyperglycemia assists in the glycation of many proteins which can enhance antigenic responses. Also, glycation promotes inflammatory responses by increasing the

production of pro-inflammatory cytokines and decreasing the production of anti-inflammatory molecules. Thus, DM can produce a state of inflammation that leads to vascular and neurovascular disease. It is now well known that inflammation in the brain eventually activates microglia, and after the activation of microglia, inflammation persists for long periods of time. Studies trying to understand this mechanism have shown that, although peripheral inflammation resolves in a matter of a few days, microgliosis takes weeks, and even months to resolve completely, therefore, causing long lasting alterations to the neural outlook (Bonds et al., 2016). Also, inflammation is associated with enhanced oxidative stress via increased production of ROS and decreased antioxidant responses, which is a hallmark of both T1DM and T2DM and a contributing factor to the development of diabetic neuropathy (Vincent et al., 2004; Russel et al., 2008; Sims-Robinson et al., 2010). Reactive oxygen species are important in the regulation of cell signaling, but when produced chronically at high levels, they alter the chemical composition of proteins, lipids, and DNA, resulting in their dysfunction. In that way, the accumulation of dysfunctional biomolecules can also lead to the impairments in the brain. Protein and lipid peroxidation induced by the action of ROS and reactive nitrogen species (RNS) results in cell damage possibly leading to neuronal death, and it is found to be increased in both DM and AD patients compared with healthy individuals (Giugliano et al., 1996; Pratico et al., 2004). Even in patients with MCI, levels of oxidized protein were found to be increased in the frontal lobe, parietal lobe and the hippocampus, compared with healthy controls (Butterfield et al., 2007). Also, it is widely accepted that the increase in the production of ROS is a leading

cause responsible for the loss of dopaminergic neurons in PD (Kim et al., 2015; Sanders & Greenamyre, 2013; Subramaniam & Chesselet, 2013).

4.5.2. Advanced Glycation End-products (AGEs)

Moreover, abnormal glucose metabolism and oxidative stress contribute to the formation of AGEs, which form normally during aging, but these processes are more pronounced in patients with diabetes, and have a special role in causing diabetic complications (Singh et al., 2001). Advanced glycation end-products (AGEs) are believed to participate in the development and progression of complications of T2DM through Receptor for AGE (RAGE) interactions. AGEs form as a result of nonenzymatic glycoxidation. This process is greatly accelerated in conditions such as T2DM and impaired glucose tolerance where there is hyperglycemia (Bonds et al., 2016).

AGEs play a significant role in the pathogenesis of chronic diabetic complications by altering cellular structure and function (DeGroot et al., 2001). Formation of AGEs on proteins causes structural distortion, loss of side chain charge, and functional impairment (Ahmed et al., 2005). AGE deposits are commonly found in atherosclerotic plaques, vascular smooth muscle, and in myocardial tissues (Sakata et al., 1995). Similarly, both AGEs and RAGE have been found in the brain of patients with AD (Smith et al., 1994; Yan et al., 1996).

In a study conducted by Sasaki et al. it has been found that AGE immunoreactivity is present in both β-amyloid and neurofibrillary tangles in patients with AD (Sasaki et al., 1998). What's more, the same study has shown that neurons from the hippocampus of these patients contain ß-amyloid positive and AGE positive granules (Sasaki et al.,

1998).

AGEs have also been found intracellularly, in the alpha-synuclein-positive Lewy bodies in the brains of both PD as well as incidental Lewy body disease patients, implicating a role of AGEs in alpha-synuclein cross-linking and Lewy body formation (Shaikh & Nicholson, 2008).

4.5.3. Mitochondrial dysfunction

Both PD and AD, as well as DM are associated with decreased mitochondrial activity (Moreira et al., 2007). Mitochondria are the main cell organelles for various cellular processes, including ATP production, intracellular Ca^{2+} signaling, free-radical scavenging, etc. Neurons largely depend on mitochondrial function because of the establishment of membrane excitability and execution of the complex processes of neurotransmission and plasticity (Kann et Kovacs, 2007).

The calcium hypothesis says that there is dysregulation of calcium homeostasis in normal aging of the brain and in age-related diseases (Khachaturian, 1994; Kostyuk et al., 2001). Uncontrolled uptake of calcium by the mitochondria leads to ROS production, inhibition of ATP synthesis, cytochrome c release and an abrupt increase in permeability of the inner mitochondrial membrane (Brustovetsky et al., 2002), leading to mitochondrial impairment and ultimately to neurodegeneration and cell death (Sims-Robinson et al., 2010).

Tissue from the brain of patients with AD showed an increase in the calcium concentration, especially in neurons containing neurofibrillary tangles, compared with healthy individuals (Murray et al., 1992).

Abnormal calcium metabolism is common in patients with diabetes, in fact, in both T1DM and T2DM there is an increase in intracellular calcium levels (Levy et al., 1994). The studies, and their findings presented here explain how cellular processes in both diseases affect one another, and even overlap frequently.

The relationship between mitochondrial dysfunction in neurons and hyperglycemia is another possible mechanism in the pathogenesis of PD. There's a theory that hyperglycemia metabolically damages the mitochondria, which leads to a defect in oxidative phosphorylation (Nishikawa et al., 2000; Brownlee, 2005; Giacco and Brownlee, 2010). Defective mitochondrial oxidative phosphorylation induces oxidative stress and ROS, which then contribute to the damage of mitochondrial DNA themselves, and it also compromises ATP synthesis capacity. Neurons largely rely on oxidative metabolism to obtain energy efficiently for their physiological functions, and mitochondria have a main role in this process (Sergi et al., 2019). Therefore, mitochondrial impairment compromises neuronal energy availability, particularly in nigrostriatal neurons, with a high energy demand, which could explain their increased susceptibility to hyperglycemia (Renaud et al., 2018).

The role of these pathways as mediators of hyperglycemia effects in the pathogenesis of PD is yet to be fully understood (Sergi et al., 2019).

5. Conclusion

The brain is a glucose-dependent organ that can be damaged by both hypoglycemia/hyperglycemia, and if we add the insulin resistance in the picture, everything becomes very complicated. Diabetes is a lifelong disease which affects multiple organ systems starting from the kidneys, to peripheral neurons to the cardiovascular system. However, we also have to take the brain into consideration and the changes that can be expected on both, the macrostructural and microstructural levels. The incidence of type 2 diabetes mellitus (T2DM) increases with age as well as neurodegeneration increases with advanced age. Recent studies have revealed that T2DM is a risk factor for cognitive and motor dysfunctions, especially those related to AD and PD. Insulin resistance, which is often associated with T2DM, may induce a deficiency of insulin effects in the central nervous system. Insulin may have a neuroprotective role and may have some impact on acetylcholine and dopaminergic signalling. Additionally, microvascular changes leading to asymptomatic ischemic lesions and damage to neurons in T2DM subjects may lower the threshold for the development of neurodegenerative diseases (Fig. 3). Taken together, insulin resistance, ischemia and irregular glucose control can all lead to the formation of AGEs, oxidative stress, mitochondrial dysfunction, inflammation and, finally, to neuronal damage. Nevertheless, the nature of brain changes in patients with diabetes is still poorly understood. Taken together, the complex systemic effects of T2DM on neurodegenerative disease such as AD and PD cannot be ignored and require further investigation. This could lead to the discovery of new treatments or preventive methods such as the incretins GLP-1

(glucagon-like peptide-1) and GIP (glucose-dependent insulinotropic polypeptide), hormones that re-sensitize insulin signalling and are already showing promising results in clinical trials.

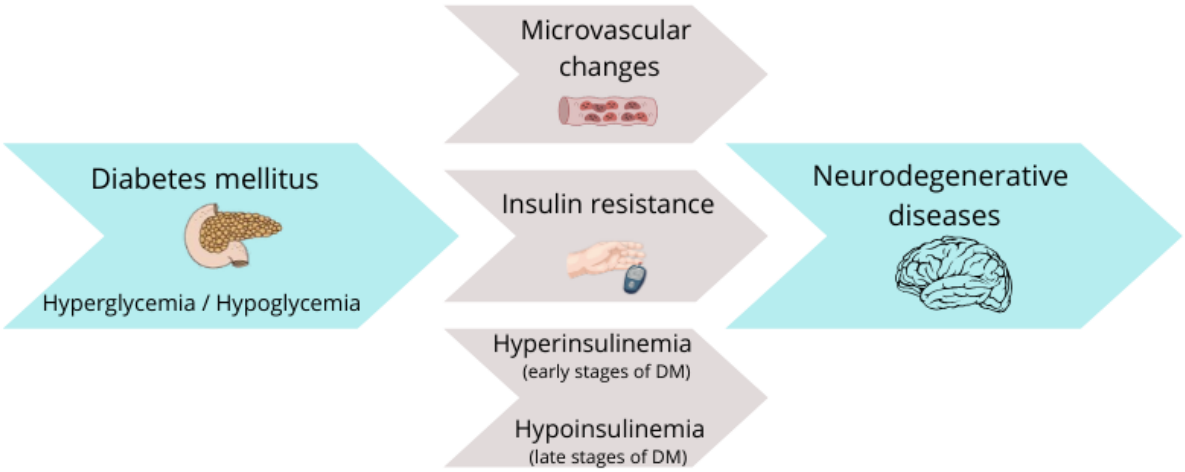

Figure 3: Microvascular changes and insulin resistance, together with hypo and hyperinsulinemia are considered to be key factors linking diabetes and neurodegenerative diseases

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7. References

1. Ahmed, N., Dobler, D., Dean, M., & Thornalley, P. J. (2005) Peptide mapping identifies hotspot site of modification in human serum albumin by methylglyoxal involved in ligand binding and esterase activity. J Biol Chem, 2005 Feb 18;280(7):5724-32. doi: 10.1074/jbc.M410973200

2. Ajaya, B., & Haranath, P. S. (1982) Effects of insulin administered into cerebrospinal fluid spaces on blood glucose in unanaesthetized and anaesthestized dogs. Indian J Med Res 75, 607–615.

3. Aminoff MJ, Greenberg DA, Simon RP (2015) Clinical neurology, 9th edition

4. Anan F, Masaki T, Kikuchi H et al. (2010) Association between plasma high-sensitivity C-reactive protein and insulin resistance and white matter lesions in Japanese type 2 diabetic patients. Diabetes Res Clin Pract 2010; 87: 233-239.

5. Athauda, D., and Foltynie, T. (2016) Insulin resistance and Parkinson's disease: a new target for disease modification? Prog. Neurobiol. 145–146, 98–120. doi: 10.1016/j.pneurobio.2016.10.001

6. Baker, L.D., Cross, D.J., Minoshima, S., Belongia, D., Watson, G.S., Craft, S. (2011) Insulin resistance and Alzheimer-like reductions in regional cerebral glucose metabolism for cognitively normal adults with prediabetes or early type 2 diabetes. Arch. Neurol. 68, 51–57. doi:http://dx.doi.org/10.1001/ archneurol. 2010.225.

7. Banks, W. A., Jaspan, J. B., Huang, W., & Kastin, A. J. (1997) Transport of insulin across the blood–brain barrier: Saturability at euglycemic doses of insulin. Peptides 18, 1423–1429.

8. Banks WA, Owen JB, Erickson MA (2012) Insulin in the brain: There and back again Pharmacology & Therapeutics 136 (2012) 82–93

9. Barbeau, A., Giguere, R., and Hardy, J. (1961) Clinical experience with tolbutamide in Parkinson's disease. Union Med. Can. 90, 147–151

10. Barilar J.O., Knezovic A., Perhoc A.B., Homolak J, Riederer P, Salkovic Petrisic M. (2020) Shared cerebral metabolic pathology in non-transgenic animal models

of Alzheimer's and Parkinson's disease, Jour of Neural Transmis 127 (2), 231-250

11. Baura, G. D., Foster, D. M., Porte, D., Jr., Kahn, S. E., Bergman, R. N., Cobelli, C., et al (1993) Saturable transport of insulin from plasma into the central nervous system of dogs in vivo: A mechanism for regulated insulin delivery to the brain. J Clin Invest 92, 1824–1830.

12. Beauquis, J., Homo-Delarche, F., Giroix, M. H., Ehses, J., Coulaud, J., Roig, P., et al. (2010) Hippocampal neurovascular and hypothalamic-pituitary-adrenal axis alterations in spontaneously type 2 diabetic GK rats. Experimental Neurology, 222, 125–134.

13. Biessels, G.J., Staekenborg, S., Brunner, E., Brayne, C. And Sheltens, P. (2006) Risk of dementia in diabetes mellitus - a systematic review, Lancet neurology 5 (64-74)

14. Biessels, G. J., van der Heide, L. P., Kamal, A., Bleys, R. L. & Gispen, w. H. (2002) Ageing and diabetes: implications for brain function. Eur. J. Pharmacol. 441, 1–14.

15. Bohnen NI, Müller ML, Zarzhevsky N, Koeppe RA, Bogan CW, Kilbourn MR, Frey KA, Albin RL (2011) Leucoaraiosis, nigrostriatal denervation and motor symptoms in Parkinson's disease.Brain. 2011 Aug; 134(Pt 8):2358-65.

16. Bonds JA, Hart PC, Minshall RD, Lazarov O, Haus JM and Bonini MG (2016) Type 2 Diabetes Mellitus as a Risk Factor for Alzheimer’s Disease, Genes, Environment and Alzheimer’s Disease, 2016, CHAPTER 13 388-413.

17. Borghammer, P., Chakravarty, M., Jonsdottir, K.Y., Sato, N., Matsuda, H., Ito, K., Arahata, Y., Kato, T., Gjedde, A. (2010) Cortical hypometabolism and hypoperfusion in Parkinson’s disease is extensive: probably even at early disease stages. Brain Struct. Funct. 214, 303–317. doi:http://dx.doi.org/10.1007/s00429-010-0246-0.

18. Bosco, D., Fava, A., Plastino, M., Montalcini, T., & Pujia, A. (2011). Possible implications of insulin resistance and glucose metabolism in Alzheimer's disease pathogenesis. J Cell Mol Med 15, 1807–1821.

19. Boyd, A. E. III., Lebovitz, H. E., and Feldman, J. M. (1971) Endocrine function and glucose metabolism in patients with Parkinson’s disease and their alternation by L-dopa. J. Clin. Endocrinol. Metab. 33, 829–837. doi: 10.1210/jcem- 33-5-829

20. Brands AM, Kessels RP, de Haan EH, Kappelle LJ, Biessels GJ (2004) Cerebral dysfunction in type 1 diabetes: effects of insulin, vascular risk factors and blood-glucose levels. Eur J Pharmacol 2004; 490: 159-168 [PMID: 15094082 DOI: 10.1016/j.ejphar.2004.02.053]

21. Brief, D. J., & Davis, J. D. (1984) Reduction of food intake and body weight by chronic intraventricular insulin infusion. Brain Res Bull 12, 571–575.

22. Brouwers, O., Niessen, P. M., Haenen, G., Miyata, T., Brownlee, M., Stehouwer, C. D., et al. (2010) Hyperglycaemia-induced impairment of endothelium-dependent vasorelaxation in rat mesenteric arteries is mediated by intracellular methylglyoxal levels in a pathway dependent on oxidative stress. Diabetologia, 53, 989–1000.

23. Brownlee, M. (2005) The pathobiology of diabetic complications: a unifying mechanism. Diabetes 54, 1615–1625. doi: 10.2337/diabetes.54.6.1615

24. Brownlee M (2001) Biochemistry and molecular cell biology of diabetic complications, Nature 414, 813-820.

25. Bruning, J. C., Gautam, D., Burks, D. J., Gillette, J., Schubert, M., Orban, P. C., et al. (2000) Role of brain insulin receptor in control of body weight and reproduction. Science (Washington DC) 289, 2122–2125.

26. Brustovetsky, N., Brustovetsky, T., Jemmerson, R. & Dubinsky, J. M. (2002) Calcium-induced cytochrome c release from CNS mitochondria is associated with the permeability transition and rupture of the outer membrane. J. Neurochem. 80, 207–218.

27. Butterfield, D. A. et al. (2007) Elevated levels of 3-nitrotyrosine in brain from subjects with amnestic mild cognitive impairment: implications for the role of nitration in the progression of Alzheimer's disease. Brain Res. 1148, 243–248.

28. Cameron NE, Eaton SE, Cotter MA, Tesfaye S (2001) Vascular factors and metabolic interactions in the pathogenesis of diabetic neuropathy. Diabetologia 2001; 44: 1973-1988 [PMID: 11719828 DOI: 10.1007/s001250100001

29. Chaudhuri KR, Yates L, Martinez-Martin P (2005) The non-motor symptom complex of Parkinson's disease: A comprehensive assessment is essential. Curr Neurol Neurosci Rep 5: 275–283

30. Cheng, B., Yang, X., An, L., Gao, B., Liu, X., and Liu, S. (2009) Ketogenic diet protects dopaminergic neurons against 6-OHDA neurotoxicity via up-regulating

glutathione in a rat model of Parkinson's disease. Brain Res. 1286, 25–31. doi: 10.1016/j.brainres.2009.06.060

31. Chung, Y. H., Shin, C. M., Joo, K. M., Kim, M. J., & Cha, C. I. (2002) Region-specific alterations in insulin-like growth factor receptor type I in the cerebral cortex and hippocampus of aged rats. Brain Res 946, 307–313.

32. Cole AR, Astellb A, Greena C, Sutherland C. (2007) Molecular connexions between dementia and diabetes, Neurosci. Biobehav. Rev. 31 1046–1063

33. Convit A, Wolf OT, Tarshish C, de Leon MJ (2003) Reduced glucose tolerance is associated with poor memory performance and hippocampal atrophy among normal elderly, Proc. Natl. Acad. Sci. U. S. A. 100 2019–2022

34. Cui, Y., Jiao, Y., Chen, Y. C., Wang, K., Gao, B., Wen, S., et al. (2014) Altered spontaneous brain activity in type 2 diabetes: a resting-state functional MRI study. Diabetes 63, 749–760. doi: 10.2337/db13-0519

35. Dauer W, Przedborski S Parkinson's disease: mechanisms and models. Neuron. 2003 Sep 11; 39(6):889-909.

36. Davidson's Principles & Practice of Medicine (Book 21), Churchill Livingstone; 21 edition (March 25, 2010)

37. Debons, A. F., Krimsky, I., & From, A. (1970). A direct action of insulin on the hypothalamic satiety center. Am J Physiol 219, 938–943.

38. de Bresser, J., Tiehuis, A. M., Van Den Berg, E., Reijmer, Y. D., Jongen, C., Kappelle, L. J., et al. (2010) Progression of cerebral atrophy and white matter hyperintensities in patients with type 2 diabetes. Diabetes Care 33, 1309–1314. doi: 10.2337/dc09-1923

39. DeGroot, J., Verzijl, N., Wenting-Van Wijk, M. J., Bank, R. A., Lafeber, F. P., Bijlsma, J. W., et al. (2001) Age-related decrease in susceptibility of human articular cartilage to matrix metalloproteinase-mediated degradation: The role of advanced glycation end products. Arthritis and Rheumatism, 2001 Nov;44(11): 2562-71

40. Demars, M., Hu, Y. S., Gadadhar, A., & Lazarov, O. (2010) Impaired neurogenesis is an early event in the etiology of familial Alzheimer's disease in transgenic mice. Journal of Neuroscience Research, 88, 2103–2117.

41. den Heijer, T., Vermeer, S. E., Van Dijk, E. J., Prins, N. D., Koudstaal, P. J., Hofman, A., et al. (2003) Type 2 diabetes and atrophy of medial temporal lobe

structures on brain MRI. Diabetologia 46, 1604–1610. doi: 10.1007/s00125-003-1235-0

42. De Pablo-Fernandez J., Goldacre R., Pakpoor J., Noyce A.J., Warner T.T. (2018) Association between diabetes and subsequent Parkinson disease A record-linkage cohort study. Neurology. 2018, 91(2):139-e142. doi: 10.1212/WNL.0000000000005771. Epub 2018 Jun 13.

43. Duarte, A. I., Moreira, P. I., and Oliveira, C. R. (2012) Insulin in central nervous system: more than just a peripheral hormone. J. Aging Res. 2012:384017. doi: 10.1155/2012/384017

44. Dunn, L., Allen, G.F., Mamais, A., Ling, H., Li, A., Duberley, K.E., Hargreaves, I.P., Pope, S., Holton, J.L., Lees, A., Heales, S.J., Bandopadhyay, R. (2014) Dysregulation of glucose metabolism is an early event in sporadic Parkinson's disease. Neurobiol. Aging 35, 1111–1115. doi:http://dx.doi.org/10.1016/j.neurobiolaging.2013.11.001.

45. Executive Summary: Standards of Medical Care in Diabetes—2014 Diabetes Care 2014 Jan; 37(Supplement 1): S5-S13. https://doi.org/10.2337/dc14-S005

46. Falvey, C. M., Rosano, C., Simonsick, E. M., Harris, T., Strotmeyer, E. S., Satterfield, S., et al. (2013) Macro- and microstructural magnetic resonance imaging indices associated with diabetes among community-dwelling older adults. Diabetes Care 36, 677–682. doi: 10.2337/dc12-0814

47. Figlewicz, D. P., Sipols, A. J., Seeley, R. J., Chaves, M., Woods, S. C., & Porte, D., Jr. (1995) Intraventricular insulin enhances the meal-suppressive efficacy of intraventricular cholecystokinin octapeptide in the baboon. Behav Neurosci 109, 567–569.

48. Florant, G. L., Richardson, R. D., Mahan, S., Singer, L., & Woods, S. C. (1991) Seasonal changes in CSF insulin levels in marmots: Insulin may not be a satiety signal for fasting in winter. Am J Physiol 260, R712–R716.

49. Folstein MF, Folstein SE, Mchugh PR (1975) Mini-mental state: a practical method for grading the cognitive state for the clinician, J. Psychiatr. Res. 12 189–198

50. Frolich, L., Blum-Degen, D., Bernstein, H. G., Engelsberger, S., Humrich, J., Laufer, S., et al. (1998) Brain insulin and insulin receptors in aging and sporadic Alzheimer's disease. J Neural Transm 105, 423–428.

51. Giacco, F., and Brownlee, M. (2010) Oxidative stress and diabetic complications. Circ. Res. 107, 1058–1070. doi: 10.1161/CIRCRESAHA.110.223545

52. Giugliano, D., Ceriello, A. & Paolisso, G. (1996) Oxidative stress and diabetic vascular complications. Diabetes Care 19, 257–267.

53. Global, regional, and national burden of neurological disorders during 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. GBD 2015 Neurological Disorders Collaborator Group

54. Global statistics on diabetes, https://www.who.int/news-room/fact-sheets/detail/diabetes

55. Grillo, C. A., Piroli, G. G., Hendry, R. M., & Reagan, L. P. (2009) Insulin-stimulated trans- location of GLUT4 to the plasma membrane in rat hippocampus is PI3-kinase dependent. Brain Res 1296, 35–45.

56. Grillo, C. A., Piroli, G. G., Kaigler, K. F., Wilson, S. P., Wilson, M. A., & Reagan, L. P. (2011) Downregulation of hypothalamic insulin receptor expression elicts depressive-like behavior in rats. Behav Brain Res 222, 230–235.

57. Hatfield, J. S., Millard, W. J., & Smith, C. J. V. (1974) Short-term influence of intra-ventromedial hypothalamic administration of insulin on feeding in normal and diabetic rats. Pharmacol Biochem Behav 2, 223–226.

58. Havrankova, J., Roth, J., & Brownstein, M. (1978) Insulin receptors are widely distributed in the central nervous system of the rat. Nature 272, 827–829.

59. Hayashi, K., Kurioka, S., Yamaguchi, T., Morita, M., Kanazawa, I., Takase, H., et al. (2011) Association of cognitive dysfunction with hippocampal atrophy in elderly Japanese people with type 2 diabetes. Diabetes Res. Clin. Pract. 94, 180–185. doi: 10.1016/j.diabres.2011.07.002

60. Herman T,Rosenberg-Katz K, Jacob Y,_Auriel E,_Gurevich T,_Giladi N,_Hausdorff JM (2013) White Matter Hyperintensities in Parkinson's Disease: Do They Explain the Disparity Between the Postural Instability Gait Difficulty and Tremor Dominant Subtypes? PLoS One 2013;8(1):e55193.

61. Hoogenboom, W. S., Marder, T. J., Flores, V. L., Huisman, S., Eaton, H. P., Schneiderman, J. S., et al. (2014) Cerebral white matter integrity and resting-state functional connectivity in middle-aged patients with type 2 diabetes. Diabetes 63, 728–738. doi: 10.2337/db13-1219

62. Horani MH, Mooradian AD (2003) Effect of diabetes on the blood brain barrier. Curr Pharm Des 2003; 9:833-40; PMID:12678883; http://dx.doi.org/10.2174/1381612033455314

63. Hosokai, Y., Nishio, Y., Hirayama, K., Takeda, A., Ishioka, T., Sawada, Y., Suzuki, K., Itoyama, Y., Takahashi, S., Fukuda, H., Mori, E. (2009) Distinct patterns of regional cerebral glucose metabolism in Parkinson's disease with and without mild cognitive impairment. Mov. Disord. 24, 854–862. doi:http://dx.doi.org/10.1002/ mds.22444.

64. Hosseini A, Abdollahi M. (2013) Diabetic neuropathy and oxidative stress: therapeutic perspectives. Oxid Med Cell Longev 2013; 2013: 168039 [PMID: 23738033 DOI: 10.1155/2013/168039]

65. Hoyer, S. (2004) Glucose metabolism and insulin receptor signal transduction in Alzheimer's disease. Eur J Pharmacol 490, 115–125.

66. Huang, C., Mattis, P., Perrine, K., Brown, N., Dhawan, V., Eidelberg, D. (2008) Metabolic abnormalities associated with mild cognitive impairment in Parkinson disease. Neurology 70, 1470–1477. doi:http://dx.doi.org/10.1212/01. wnl.0000304050.05332.9c.

67. Imamine, R., Kawamura, T., Umemura, T., Umegaki, H., Kawano, N., Hotta, M., et al. (2011) Does cerebral small vessel disease predict future decline of cognitive function in elderly people with type 2 diabetes? Diabetes Res. Clin. Pract. 94, 91–99. doi: 10.1016/j.diabres.2011.06.014

68. International Diabetes Federation. IDF Diabetes Atlas, 8th edn. Brussels, Belgium: International Diabetes Federation, 2017. http://www.diabetesatlas.org

69. Janson, J., Laedtke, T., Parisi, J. E., O'Brien, P., Petersen, R. C., & Butler, P. C. (2004) Increased risk of type 2 diabetes in Alzheimer disease. Diabetes, 53, 474–481.

70. Jash K., Gondaliya P., Kirave P., Kulkarni B., Sunkaria A., Kalia K. (2019) Cognitive dysfunction: A growing link between diabetes and Alzheimer's disease. Drug Development research Volume81, Issue 2, Special Issue: Alzheimer's Disease Therapeutics, April 2020, 144-164.

71. Jobst, K. A., Smith, A. D., Szatmari, M., Esiri, M. M., Jaskowski, A., Hindley, N., et al. (1994) Rapidly progressing atrophy of medial temporal lobe in Alzheimer's disease. Lancet 343, 829–830. doi: 10.1016/S0140-6736(94) 92028-1

72. Johnson PC, Brendel K, Meezan E. (1982) Thickened cerebral cortical capillary basement membranes in diabetics. Arch Pathol Lab Med 1982; 106: 214-217 [PMID: 6896132]

73. Jongen, C., Van Der Grond, J., Kappelle, L. J., Biessels, G. J., Viergever, M. A., Pluim, J. P., et al. (2007) Automated measurement of brain and white matter lesion volume in type 2 diabetes mellitus. Diabetologia 50, 1509–1516. doi: 10.1007/s00125-007-0688-y

74. Kann O, and Kovács R (2007) Mitochondria and neuronal activity - https://doi.org/10.1152/ajpcell.00222.2006

75. Khachaturian, Z. S. (1994) Calcium hypothesis of Alzheimer's disease and brain aging. Ann. NY Acad. Sci. 747, 1–11.

76. Kim GH, Kim JE, Rhie SJ and Yoon S: (2015) The role of oxidative stress in neurodegenerative diseases. Exp Neurobiol. 24:325–340.

77. Kodi CT, Seaquist ER (2008) Cognitive Dysfunction and Diabetes Mellitus, Endocr Rev. 2008 Jun; 29(4): 494-511.

78. Kohen Avramoglu, R., Laplante, M. A., Le Quang, K., Deshaies, Y., Despres, J. P., Larose, E., et al. (2013) The genetic and metabolic determinants of cardiovascular complications in type 2 diabetes: Recent insights from animal models and clinical investigations. Canadian Journal of Diabetes, 37, 351–358.

79. Kostyuk, E. et al. (2001) Diabetes-induced changes in calcium homeostasis and the effects of calcium channel blockers in rat and mice nociceptive neurons. Diabetologia 44, 1302–1309.

80. Kovacs GG, Alafuzoff I (2017) Concepts and classification of neurodegenerative diseases, Kovacs 2017, Handbook of Clinical Neurology, vol. 145, 3rd series, Chapter 21

81. Kushner, J.A., (2013) The role of aging upon b cell turnover. J. Clin. Invest. 123, 990– 995. doi:http://dx.doi.org/10.1172/JCI64095.

82. Lazarov, O., Mattson, M. P., Peterson, D. A., Pimplikar, S. W., & van Praag, H. (2010) When neurogenesis encounters aging and disease. Trends in Neurosciences, 33, 569–579.

83. Lazarov O., Tesco G. (2016) Genes, Environment and Alzheimer's Disease,1st Edition, Academic Press, eBook ISBN: 9780128028858

84. Levin, B.E. (2000) Glucose-regulated dopamine release from substantia nigra neurons. Brain Res. 874, 158–164.

85. Levy, J., Gavin, J. R. 3rd & Sowers, J. R. (1994) Diabetes mellitus: a disease of abnormal cellular calcium metabolism? Am. J. Med. 96, 260–273.

86. Li, W., Prakash, R., Kelly-Cobbs, A. I., Ogbi, S., Kozak, A., El-Remessy, A. B., et al. (2010) Adaptive cerebral neovascularization in a model of type 2 diabetes: Relevance to focal cerebral ischemia. Diabetes, 59, 228–235.

87. Liepelt, I., Reimold, M., Maetzler, W., Godau, J., Reischl, G., Gaenslen, A., Herbst, H., Berg, D. (2009) Cortical hypometabolism assessed by a metabolic ratio in Parkinson's disease primarily reflects cognitive deterioration-[18F]FDG-PET. Mov. Disord. 24, 1504–1511. doi:http://dx.doi.org/10.1002/mds.22662.

88. Liu, Y., Liu, F., Grundke-Iqbal, I., Iqbal, K. & Gong, C.-X. (2009) Brain glucose transporters, O-GlcNAcylation and phosphorylation of tau in diabetes and Alzheimer disease. J. Neurochem. 111, 242–249.

89. Luchsinger J.A. ,Tang M.X., Shea S., Mayeux R. (2004) Hyperinsulinemia and risk of Alzheimer disease, Neurology 63, 1187-1192.

90. Manschot, S. M., Brands, A. M., Van Der Grond, J., Kessels, R. P., Algra, A., Kappelle, L. J., et al. (2006) Brain magnetic resonance imaging correlates of impaired cognition in patients with type 2 diabetes. Diabetes 55, 1106–1113. doi: 10.2337/diabetes.55.04.06.db05-1323

91. Mathis CA, Wang Y, Holt DP, Huang GF, Debnath ML, Klunk WE (2003) Synthesis and evaluation of 11C-labeled 6-substituted 2-arylbenzothiazoles as amyloid imaging agents. J Med Chem. 2003 Jun 19; 46(13):2740-54.

92. McEwen, B. S., & Reagan, L. P. (2004) Glucose transporter expression in the central nervous system: Relationship to synaptic function. Eur J Pharmacol 490, 13–24.

93. McKusick VA, et al (2004) Online Mendelian inheritance in man (OMIM). McKusick-Nathans Institute for Genetic Medicine, Johns Hopkins University, National Center for Biotechnology Information, National Library of Medicine, Bethesda (http://www.ncbi.nlm.nih.gov/omim/)

94. Moran, C., Phan, T. G., Chen, J., Blizzard, L., Beare, R., Venn, A., et al. (2013) Brain atrophy in type 2 diabetes: regional distribution and influence on cognition. Diabetes Care 36, 4036–4042. doi: 10.2337/dc13-0143

95. Moroo, I., Yamada, T., Makino, H., Tooyama, I., McGeer, P.L., McGeer, E.G., Hirayama, K. (1994) Loss of insulin receptor immunoreactivity from the substantia nigra pars compacta neurons in Parkinson's disease. Acta Neuropathol. 87, 343–348.

96. Morris, J.K., Vidoni, E.D., Perea, R.D., Rada, R., Johnson, D.K., Lyons, K., Pahwa, R., Burns, J.M., Honea, R.A. (2014) Insulin resistance and gray matter volume in neurodegenerative disease. Neuroscience 270, 139–147. doi:http://dx.doi.org/ 10.1016/j.neuroscience.2014.04.006.

97. Murakami, K., Miyake, Y., Sasaki, S., Tanaka, K., Fukushima, W., Kiyohara, C., et al. (2010) Dietary glycemic index is inversely associated with the risk of Parkinson's disease: a case-control study in Japan. Nutrition 26, 515–521. doi: 10.1016/j.nut.2009.05.021

98. Murray, F. E., Landsberg, J. P., Williams, R. J., Esiri, M. M. & watt, F. (1992) Elemental analysis of neurofibrillary tangles in Alzheimer's disease using proton-induced X-ray analysis. Ciba Found. Symp. 169, 201–210.

99. Musen, G., Jacobson, A. M., Bolo, N. R., Simonson, D. C., Shenton, M. E., McCartney, R. L., et al. (2012) Resting-state brain functional connectivity is altered in type 2 diabetes. Diabetes 61, 2375–2379. doi: 10.2337/db11-1669

100. Nelson, T. J., Sun, M. K., Hongpaisan, J., & Alkon, D. L. (2008). Insulin, PKC signaling pathways and synaptic remodeling during memory storage and neuronal repair. Eur J Pharmacol 585, 76–87.

101. Nishikawa, T., Edelstein, D., Du, X. L., Yamagishi, S., Matsumura, T., Kaneda, Y., et al. (2000) Normalizing mitochondrial superoxide production blocks three pathways of hyperglycaemic damage. Nature 404, 787–790. doi: 10.1038/35008121

102. Nunley, K. A., Ryan, C. M., Orchard, T. J., Aizenstein, H. J., Jennings, J. R., Ryan, J., ... Rosano, C. (2015) White matter hyperintensities in middle- aged adults with childhood-onset type 1 diabetes. Neurology, 84(20), 2062-2069 https://doi.org/10.1212/wnl.0000000000001582Â

103. Peila, R., Rodriguez, B. L. & Launer, L. J. (2002) Type 2 diabetes, APOE gene, and the risk for dementia and related pathologies: The Honolulu–Asia Aging Study. Diabetes 51, 1256–1262.

104. Peppard, R.F., Martin, W.R., Carr, G.D., Grochowski, E., Schulzer, M., Guttman, M., McGeer, P.L., Phillips, A.G., Tsui, J.K., Calne, D.B. (1992) Cerebral glucose

metabolism in Parkinson’s disease with and without dementia. Arch. Neurol. 49, 1262–1268.

105. Pi, J., Bai, Y., Daniel, K. W., Liu, D., Lyght, O., Edelstein, D., et al. (2009) Persistent oxida- tive stress due to absence of uncoupling protein 2 associated with impaired pancreatic beta-cell function. Endocrinology, 150, 3040–3048.

106. Piaceri I, Nacmias B, Sorbi S (2013) Genetics of Familial and Sporadic Alzheimer's Disease. Front Biosci 2013 Jan 1;5:167-77. doi: 10.2741/e605.

107. Poduslo, J. F., Curran, G. L., & Berg, C. T. (1994) Macromolecular permeability across the blood-nerve and blood–brain barrier. Proc Natl Acad Sci U S A 91, 5705–5709.

108. Prakash, R., Johnson, M., Fagan, S. C., & Ergul, A. (2013) Cerebral neovascularization and remodeling patterns in two different models of type 2 diabetes. PLoS One, 8, e56264.

109. Pratico, D. & Sung, S. (2004) Lipid peroxidation and oxidative imbalance: early functional events in Alzheimer’s disease. J. Alzheimers Dis. 6, 171–175.

110. Reijmer, Y. D., Brundel, M., De Bresser, J., Kappelle, L. J., Leemans, A., Biessels, G. J., et al. (2013) Microstructural white matter abnormalities and cognitive functioning in type 2 diabetes: a diffusion tensor imaging study. Diabetes Care 36, 137–144. doi: 10.2337/dc12-0493

111. Renaud, J., Bassareo, V., Beaulieu, J., Pinna, A., Schlich, M., Lavoie, C., et al. (2018) Dopaminergic neurodegeneration in a rat model of long-term hyperglycemia: preferential degeneration of the nigrostriatal motor pathway. Neurobiol. Aging 69, 117–128. doi: 10.1016/j.neurobiolaging.2018.05.010

112. Ristow M (2004) Neurodegenerative disorders associated with diabetes mellitus - Journal of molecular medicine, 2004, 82/8, 510-529

113. Roriz-Filho JS, Sá-Roriz TM, Rosset I, Camozzato AL, Santos AC, Chaves MLF, Moriguti JC, Roriz-Cruz M (2009) (Pre)Diabetes, brain aging and cognition, Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease Volume 1792, Issue 5, May 2009, 432-443

114. Russell, J. w. et al. (2008) Oxidative injury and neuropathy in diabetes and impaired glucose tolerance. Neurobiol. Dis. 30, 420–429.

115. Sakata, N., Meng, J., Jimi, S., & Takebayashi, S. (1995) Nonenzymatic glycation and extract- ability of collage in human atherosclerotic plaques. Atherosclerosis , 116, 63-75

116. Sanders LH and Greenamyre JT (2013) Oxidative damage to macromolecules in human Parkinson disease and the rotenone model. Free Radic Biol Med. 62:111–120.

117. Sasaki, N. et al. (1998) Advanced glycation end products in Alzheimer's disease and other neurodegenerative diseases. Am. J. Pathol. 153, 1149–1155.

118. Schwab, R. S. (1960) Progression and prognosis in Parkinson's disease. J. Nerv. Ment. Dis. 130, 556–566. doi: 10.1097/00005053-196006000- 00017

119. Schwartz, M. W., Bergman, R. N., Kahn, S. E., Taborsky, G. L., Jr., Fisher, L. D., Sipols, A. J., et al. (1991) Evidence for entry of plasma insulin into cerebrospinal fluid through an intermediate compartment in dogs. J Clin Invest 88, 1272–1281.

120. Schwartz, M. W., Figlewicz, D. P., Baskin, D. G., Woods, S. C., & Porte, D., Jr. (1992) Insulin in the brain: A hormonal regulator of energy balance. Endocr Rev 13, 387–414.

121. Sergi D, Renaud J, Simola N and Martinoli MG (2019) Diabetes, a Contemporary Risk for Parkinson's Disease: Epidemiological and Cellular Evidences Frontiers in aging neuroscience, 08 November 2019 doi: 10.3389/fnagi.2019.00302

122. Shaikh s, Nicholson LFB (2008) Advanced Glycation End Products Induce in Vitro Cross-Linking of Alpha-Synuclein and Accelerate the Process of Intracellular Inclusion Body Formation. J Neurosci Res 2008 Jul;86(9):2071-82. doi: 10.1002/jnr.21644.

123. Sharma, S. K., Chorell, E., Steneberg, P., Vernersson-Lindahl, E., Edlund, H., and Wittung-Stafshede, P. (2015) Insulin-degrading enzyme prevents α-synuclein fibril formation in a nonproteolytical manner. Sci. Rep. 5:12531. doi: 10.1038/srep12531

124. Silvestre, J. S., & Levy, B. I. (2006) Molecular basis of angiopathy in diabetes mellitus. Circulation Research, 98, 4–6.

125. Sims-Robinson C. Bhumso K, Rosko A, Feldman EL (2010) How does diabetes accelerate Alzheimer disease pathology? Nat. Rev. Neurol. 6, 551–559

126. Singh, R., Barden, A., Mori, T. & Beilin, L. (2001) Advanced glycation end-products: a review. Diabetologia 44, 129–146.

127. Singleton R, Smith AG (2006) Therapy insight: neurological complications of pre-diabetes, Nat. Clin. Pract. Neurol. May 2 (5) (2006) 276–282

128. Smith, M. A., Taneda, S., Richey, P. L., Miyata, S., Yan, S. D., Stern, D., et al. (1994) Advanced maillard reaction end products are associated with Alzheimer disease pathology. Proceedings of the National Academy of Sciences of the United States of America, 91, 5710–5714.

129. Stadler, K. (2012) Oxidative stress in diabetes. Advances in Experimental Medicine and Biology, 771, 272–287.

130. Stafstrom, C. E., and Rho, J. M. (2012) The ketogenic diet as a treatment paradigm for diverse neurological disorders. Front. Pharmacol. 3:59. doi: 10.3389/fphar. 2012.00059

131. Steinbusch H.W.M., Schram M.T., Stehouwer C.D.A.,Wildberger J.E. and Jansen J.F.A. (2017) Cerebral Pathology and Cognition in Diabetes: The Merits of Multiparametric Neuroimaging Frontiers in Neuroscience 11:188 · April 2017 DOI: 10.3389/fnins.2017.00188

132. Strubbe, J. H., & Mein, C. G. (1977) Increased feeding in response to bilateral injection of insulin antibodies in the VMH. Physiol Behav 19, 309–313.

133. Subramaniam SR and Chesselet MF (2013) Mitochondrial dysfunction and oxidative stress in Parkinson's disease. Prog Neurobiol. 106–107:17–32.

134. Takahashi, M., Yamada, T., Tooyama, I., Moroo, I., Kimura, H., Yamamoto, T., et al. (1996) Insulin receptor mRNA in the substantia nigra in Parkinson’s disease. Neurosci. Lett. 204, 201–204. doi: 10.1016/0304-3940(96)12357-0

135. Talbot, K., Wang, H.-Y. (2014) The nature, significance, and glucagon-like peptide-1 analog treatment of brain insulin resistance in Alzheimer’s disease. Alzheimers. Dement. 10, S12–S25. doi:http://dx.doi.org/10.1016/j.jalz. 2013.12.007.

136. Tamura Y and Araki A (2015) Diabetes mellitus and white matter hyperintensity Geriatr Gerontol Int 2015; 15 (Suppl. 1): 34-42

137. Tiehuis, A., Van Der Meer, F., Mali, W., Pleizier, M., Biessels, G. J., Kappelle, J., et al. (2010) MR spectroscopy of cerebral white matter in type 2 diabetes; no association with clinical variables and cognitive performance. Neuroradiology 52, 155–161. doi: 10.1007/s00234-009-0598-4

138. Tofts, P. (2003) Quantitative MRI of the Brain Measuring Changes Caused by Disease. Chichester; Hoboken: John Wiley & Sons Ltd.

139. Unger, J., McNeill, T. H., Moxley, R. T., III, White, M., Moss, A., & Livingston, J. N. (1989). Distribution of insulin receptor-like immunoreactivity in the rat forebrain. Neuro- science 31, 143–157.

140. Van Bussel, F. C., Backes, W. H., Hofman, P. A., Van Boxtel, M. P., Schram, M. T., Stehouwer, C. D., et al. (2016b) Altered hippocampal white matter connectivity in Type 2 Diabetes Mellitus and memory decrements. J. Neuroendocrinol. 28, 12366. doi: 10.1111/jne.12366

141. Van Bussel F.C.G, Backes W.H., Hofman P.A.M., van Oostenbrugge R.J.,van Boxtel M.P.J.,Verhey F.R.J.,

142. van Elderen, S. G., De Roos, A., De Craen, A. J., Westendorp, R. G., Blauw, G. J., Jukema, J. W., et al. (2010) Progression of brain atrophy and cognitive decline in diabetes mellitus: a 3-year follow-up. Neurology 75, 997–1002.

143. van Harten, B., Oosterman, J., Muslimovic, D., Van Loon, B. J., Scheltens, P., and Weinstein, H. C. (2007) Cognitive impairment and MRI correlates in the elderly patients with type 2 diabetes mellitus. Age Ageing 36, 164–170. doi: 10.1093/ageing/afl180

144. Verdile G., Fuller S.J., Martins R.N. (2015) The role of type 2 diabetes in neurodegeneration, Neurobiol. Dis 2015 Dec;84:22-38. doi: 10.1016/j.nbd. 2015.04.008.Epub 2015 Apr 26.

145. Vincent, A. M., Russell, J. w., Low, P. & Feldman, E. L. (2004) Oxidative stress in the pathogenesis of diabetic neuropathy. Endocr. Rev. 25, 612–628.

146. Wardlaw, J. M., Smith, E. E., Biessels, G. J., Cordonnier, C., Fazekas, F., Frayne, R., et al. (2013). Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. Lancet Neurol. 12, 822-838. doi: 10.1016/S1474-4422(13)70124-8Â

147. Weller J,Budson A (2018) Current understanding of Alzheimer's disease diagnosis and treatment. F1000Res. 2018; 7: F1000 Faculty Rev-1161

148. White L, Petrovitch H, Hardman J, Nelson J, Davis D.G., Ross G.W.,Masaki K, Launer L, Markesbery W.R. (2002) Cerebrovascular pathology and dementia in autopsied Honolulu-Asia Aging Study participants, Ann. N. Y. Acad. Sci. 977 9–23.

149. Wild A.S. , Roglic G., Green A., Sicree R., King H. (2004) Global prevalence of diabetes: estimates for the year 2000 and projections for 2030, Diabetes Care 27, 1047-1053

150. Willette, A.A., Bendlin, B.B., Starks, E.J., Birdsill, A.C., Johnson, S.C., Christian, B.T., Okonkwo, O.C., La Rue, A., Hermann, B.P., Koscik, R.L., Jonaitis, E.M., Sager, M.A., Asthana, S. (2015a) Association of insulin resistance with cerebral glucose uptake in late middle-aged adults at risk for Alzheimer disease. JAMA Neurol. doi:http://dx.doi.org/10.1001/jamaneurol.2015.0613.

151. Willette, A.A., Johnson, S.C., Birdsill, A.C., Sager, M.A., Christian, B., Baker, L.D., Craft, S., Oh, J., Statz, E., Hermann, B.P., Jonaitis, E.M., Koscik, R.L., La Rue, A., Asthana, S., Bendlin, B.B., (2015b) Insulin resistance predicts brain amyloid deposition in late middle-aged adults. Alzheimers Dement. 11, 504–510. doi:http://dx.doi.org/ 10.1016/j.jalz.2014.03.011 e1

152. Woods, S. C., & Porte, D., Jr. (1983) The role of insulin as a satiety factor in the central nervous system. In A. J. Szabo (Ed.), Advances in Metabolic Disorders, CNS Regulation of Carbohydrate Metabolism, vol. 10 (pp. 457–482). New York: Academic Press.

153. Xia, W., Wang, S., Sun, Z., Bai, F., Zhou, Y., Yang, Y., et al. (2013) Altered baseline brain activity in type 2 diabetes: a resting-state fMRI study. Psychoneuroendocrinology 38, 2493–2501. doi: 10.1016/j.psyneuen. 2013.05.012

154. Xiong, Y., Sui, Y., Xu, Z., Zhang, Q., Karaman, M. M., Cai, K., et al. (2016) A diffusion tensor imaging study on white matter abnormalities in patients with type 2 diabetes using tract-based spatial statistics. AJNR Am. J. Neuroradiol. 37, 1462–1469. doi: 10.3174/ajnr.A4740

155. Yaffe K, Blackwell T, Kanaya AM, Davidowitz N, Barrett-Connor E, Krueger K (2004) Diabetes, impaired fasting glucose, and development of cognitive impairment in older women, Neurology 63 658–663

156. Yan, S. D., Chen, X., Fu, J., Chen, M., Zhu, H., Roher, A., et al. (1996) RAGE and amyloid- beta peptide neurotoxicity in Alzheimer's disease. Nature, 382, 685–691.

157. Yang, X., and Cheng, B. (2010) Neuroprotective and anti-inflammatory activities of ketogenic diet on MPTP-induced neurotoxicity. J. Mol. Neurosci. 42, 145–153. doi: 10.1007/s12031-010-9336-y

158. Yau, P. L., Javier, D., Tsui, W., Sweat, V., Bruehl, H., Borod, J. C., et al. (2009) Emotional and neutral declarative memory impairments and associated white matter microstructural abnormalities in adults with type 2 diabetes. Psychiatry Res. 174, 223–230. doi: 10.1016/j.pscychresns.2009.04.016

159. Yong, S.W., Yoon, J.K., An, Y.S., Lee, P.H. (2007) A comparison of cerebral glucose metabolism in Parkinson's disease, Parkinson's disease dementia and dementia with Lewy bodies. Eur. J. Neurol. 14, 1357–1362. doi:http://dx.doi.org/10.1111/ j.1468-1331.2007.01977.x.

160. Zhang, J., Liu, Z., Li, Z., Wang, Y., Chen, Y., Li, X., et al. (2016) Disrupted white matter network and cognitive decline in type 2 diabetes patients. J. Alzheimers. Dis. 53, 185–195. doi: 10.3233/JAD-160111

161. Zhang, J., Wang, Y., Wang, J., Zhou, X., Shu, N., Wang, Y., et al. (2014) White matter integrity disruptions associated with cognitive impairments in type 2 diabetic patients. Diabetes 63, 3596–3605. doi: 10.2337/db14-0342

162. Zhang, Y., Zhang, X., Zhang, J., Liu, C., Yuan, Q., Yin, X., et al. (2014) Gray matter volume abnormalities in type 2 diabetes mellitus with and without mild cognitive impairment. Neurosci. Lett. 562, 1–6. doi: 10.1016/j.neulet.2014.01.006

163. Zhao, W.-Q., Chen, H., Quon, M.J., Alkon, D.L. (2004) Insulin and the insulin receptor in experimental models of learning and memory. Eur. J. Pharmacol. 490, 71–81. doi:http://dx.doi.org/10.1016/j.ejphar.2004.02.045.

164. Zhao C., Deng W., Gage F. H. (2008) Mechanisms and functional implications of adult neurogenesis. Cell. 2008;132(4):645–660. doi: 10.1016/j.cell.2008.01.033. PMID: 18335520 DOI: 10.1002/jnr.21644

165. Zheng, F., Yan, L., Yang, Z., Zhong, B., & Xie, W. (2018) HbA1c, diabetes and cognitive decline: The English longitudinal study of ageing. Diabetologia, 61(4), 839–848. https://doi.org/10.1007/s00125-017-4541-7

166. Zheng Y, Ley SH, Hu FB (2017) Global etiology and epidemiology of type 2 diabetes mellitus and its complications, Nat Rev Endocrinol. 2018 Feb;14(2): 88-98. doi: 10.1038/nrendo.2017.151. Epub 2017 Dec

167. Zhou, H., Lu, W., Shi, Y., Bai, F., Chang, J., Yuan, Y., et al. (2010) Impairments in cognition and resting-state connectivity of the hippocampus in elderly subjects with type 2 diabetes. Neurosci. Lett. 473, 5–10. doi: 10.1016/j.neulet.2009.12.057

8. Biography

Laura Tomić is a final year medical student at the School of Medicine, University of Zagreb, born in Zagreb, Croatia.

She believes in a holistic approach to medicine and is interested in longevity and preventive medicine, through different clinical fields and research.

From early on, she has been interested in the human body and its potency, and that was her primary motivation in pursuing medical studies.

However, at one point she was considering studying English and French, since she is fluent in both languages and loves to learn about other cultures through languages. That’s where Medical Studies in English came into the picture, and she’s very grateful for that opportunity.

She likes to experiment with different dietary approaches and exercise, and she’s hoping that one day she will be researching these fields and their effects on human health and wellbeing.