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POTENTIAL RISK FACTORS OF THE COGNITIVE DYSFUNCTION IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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Abstract

It is known that the aged persons with type 2 diabetes mellitus present a high risk for developing neurocognitive disorders and in order to explain this phenomenon we have proposed some potential risk factors. They can be involved in the causality patterns or can act as useful markers of the cerebrovascular lesions (or both) and for which there are strong proofs, including the poor glycemic control, hypoglycemia, microvascular diseases, inflammation or depression. For the macrovascular affections, the association with the cognitive disorders seems to devolve on the examined vascular system. It is put into discussion that for the next researches it is important to analyze how exactly the interrelations between the risk factors can contribute to cognitive disorders.

key words: *diabetes mellitus, risk factors, neurocognitive disorders*

Background and aims

The global outbreak of the diabetes mellitus generates a more important burden on the health systems. The incidence of dementia begins to spread globally. The diabetes – characterized by chronic hyperglycemia – seems to be associated with a high risk of Alzheimer's disease (AD) and vascular dementia (VD) in the general population [1], and in case of the persons already diagnosed with a slight cognitive disorder they are correlated with age [2]. As regards the cognitive aging at persons diagnosed with type 2 diabetes (T2DM) existing data shows an accelerated cognitive decline in a prevalence of 20-50 % [3], and in the same time, the studies suggested that T2DM developed earlier, plays an important role in developing the cognitive decline [4]. The most affected seem to be the aspects belonging to the affectation of the frontal lobe, more specifically the psychomotor disorders, processing speed and the executive function [5].

Many psychosocial, metabolic and vascular factors play a significant role in developing the neurocognitive disorders at patients with diabetes mellitus and can contribute to the cognitive deterioration in association with T2DM. The majority of the factors are interdependent and could influence the cognitive capacity by the agency of different physio pathological ways. It is of great importance to underline that even in the case where the associations based on observational reviews are well established, they do not demonstrate the causality, and therefore to the assessment of the

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epidemiological evidences has been added the studying of the interventions. Many of the risk factors are susceptible of affecting knowledge through an influence on the cerebrovascular malady, on the pathology of the AD-typical or on both [6,9].

Vascular and metabolic risk factors

Dyslipidemia

The neurocognitive function has been reported as being significantly weaker in persons with T2DM who present increased plasma levels of triglycerides and with the ones with higher levels of cholesterol [7], but none of these observations has been confirmed [8,10].

Despite the obvious beneficial effects that the statins have on the patients suffering of heart diseases, there are theories affirming that these medications could have cognitive side effects, such as: memory loss, impaired thinking and learning difficulties – symptoms that could erroneously classified as dementia.

Although a high level of cholesterol in the blood generates a milieu favorable for heart affections, it plays in the brain an important role in forming the neuronal connections and in accelerating the electric impulses [33].

In the randomized controlled trial (RCT), ACCORD-MIND, up to 3,000 aged persons with T2DM have been distributed either to the intensive treatment of hyperglycemia or to the standard therapy [15]. Approximately a half of the participants have entered into the same randomized trial up to now in order to approach the effects of reducing the levels of plasmatic lipids on the cognitive impairment in the persons with T2DM, the other candidates participating in an antihypertensive study. Despite a bigger reduction of the level of cholesterol in the patients receiving fenofibrate and simvastatin, in comparison with the ones being administered placebo and simvastatin, the cognitive function in the two groups has decreased at similar rates as a follow-up period of 40 months [15].

Hypertension

Hypertension is frequent in persons with T2DM and, generally speaking, it was paid more attention to it than to dyslipidemia as a risk factor for the cognitive decline associated with diabetes. The transversal studies have highlighted tendencies in the increasing of the hypertension's prevalence in the patients with cognitive dysfunction [8,11,17]. Certain prospective studies [12,17,19] have ascertained a relation between the initial blood pressure or the hypertension and the subsequent risk of cognitive deterioration. In the Fremantle Diabetes study, the initial raised blood pressure was associated with a high risk of occurrence of the Alzheimer's disease after 8 years [12], and in the case of an investigation performed to persons of over 80 years old, the coexistence of the hypertension shows the aggravation of the cognitive decline and the dementia risk in the persons with diabetes during a 6-year follow-up [17]. Therefore, hypertension causes cerebrovascular illness which means it represents an important risk factor for cognitive disease.

Hypoglycemia

Few researches have investigated the effect of the anterior exposure to recurrent hypoglycemia on the cognitive function in the persons with T2DM.

A series of studies has reported an association between the antecedents of the anterior severe hypoglycemia – self-reported or verified medically and defined as any episode needing external help for improvement – and the cognitive dysfunction [12], and this could reflect the cognitive ability of the persons continuing to suffer from repeated severe hypoglycemia.

In Edinburgh Type 2 Diabetes Study (ET2DS), with more than 1,000 candidates aged between 60-75, a medical record of severe hypoglycemia has been associated with an altered cognitive function when the pre-morbid cognitive function estimated before the exposure to hypoglycemia has been compared with the cognitive function after the exposure to hypoglycemia, existing evidence of acceleration in the cognitive function at the end of life, which has been independent of the potential influence of the additional hypoglycemia episodes [29].

Two retrospective investigations [27,28] have suggested a connection between the exposure frequency to the severe hypoglycemia and the ulterior endanger of dementia. Nevertheless, the studies were based on the hospital documents – a sub-optimal method for identifying the hypoglycemia – and the suggestion that the exposure to even a single hypoglycemia episode would induce dementia is implausible.

Hyperglycemia

The raised values of glycaemia in the pre or non-diabetic interval have been constantly associated with the cognitive dysfunction – an association made along with aging [22]. The results from the transversal analyses concerning the association HbA1c with the cognitive function [7,8,11,12,14,18] and the cognitive decline [10,12,15] in the persons with type 2 diabetes mellitus have been inconsistent.

Hyperinsulinemia

The hyperinsulinemia from the endogenous hypersecretion usually appears at the onset of type 2 diabetes as a "pathophysiological" reaction to insulin. It also appears as a repercussion of the exogenous insulin therapy. The hyperinsulinemia has been associated with the cognitive dysfunction, but a systematic revision of the observational studies - including the persons with and without diabetes mellitus - has reached the conclusion that the evidences for an association of the increased concentrations of plasmatic insulin with the affectation of knowledge have decreased, because it is possible that any association of plasmatic insulin with cognition in such evidences could have been influenced by the inclusion of the persons with diabetes mellitus [21]. The interrelations between the insulin's plasmatic concentration, quality of glycaemia control and the resistance to insulin keep on complicating the attempts to evaluate the association of any of these risk factors with the cognitive decline [31].

Inflammation

The low-level chronic inflammation is also a feature of the diabetes and of the Alzheimer dementia and seems to interact with diabetes in association with the cognitive disorders. This fact suggests a common biologic mechanism [26]. The inflammatory biomarkers include C-reactive protein (CRP), interleukine-6 (IL-6), tumor necrosis factor-alpha (TNF-α) and fibrinogen, some of them being associated with the cognitive dysfunction in diabetes [31]. A series of studies has been carried out concerning the relation between the anti-inflammatory, non-steroidal, but also steroidal drugs used as treatment in the inflammatory affections and Alzheimer's disease; these studies indicate that the persons undergoing this long-term treatment could have a risk of up to 50% lower to develop this type of dementia [34].

Microvascular disease

As a result of the homology between the cerebrovascular and retinal cells, the condition of small vessels in the retina reflects firmly the cerebral microvascularisation, implying that the diabetic retinopathy can be used as feature for the presence of cerebral microangiopathy. Thus, the diabetic retinopathy can be a presumed

surrogate marker for cognitive disorders in the patients with diabetes mellitus, where the cerebral microvascular disease can play a significant pathogen role [31].

The cerebrovascular disease and the carotid intima and adventitial thickening

As regards the stroke, the age seems to be the most relevant risk factor. There are minimum gender related differences, the men being subject to a higher risk to this effect [35]. A possible explanation could be that the estrogen would exercise a protective role on the brain by increasing the cerebral blood flow, stimulating the cholinergic system, preventing the cerebral atrophy and the reversing of lesions caused by glucocorticoids, as it was revealed by the studies carried out on murine models, respectively the researches made on postmenopausal women who had received estrogenic replacement therapy [34]. The risk factors also include the hypertension, smoking, diabetes, obesity and alcohol consumption [35].

In a study elaborated in 1996 by Censori et al., 25% of the 304 hospitalized patients with strokes – 146 of them being at their first presentation - got into dementia in the following 3 months. The strongest predictors for the commencement of dementia within this test sample have been: diabetes, atrial fibrillation, aphasia and infarcts at the level of the middle cerebral artery [34].

In ET2DS study and in Fremantle Diabetes Study, a history of the stroke has been associated with a more accentuated diminishing of the cognitive ability [12,25], but this observation has been different than the one of the many other prospective analyses [18]. No links have been found. In the ADVANCE study, there were noticed evidences of a prospective association with lower cognitive functions which make the patients more amenable to an increased risk of heart failure. In the case of persons with T2DM, a larger thickness of the carotid intima-media (cIMT) has been associated with a diminished level of the cognitive function [7, 8], but its association with an estimated sudden decrease of the cognitive function during a lifetime has been inconstant [22,25]. In a general way, among the population it was established an association between a larger cMIT and an increased risk of cognitive insufficiency [24], so that a similar association can also exist in the case of persons with T2DM.

Coronary disease and the N-terminal Pro-brain natriuretic peptide

In ET2DS study [25] has been noticed a connection between the coronary disease and the cognitive dysfunction, but in the study ACCORD-MIND, the association between the coronary disease and the cognitive dysfunction has been limited [10]. Also in other transversal researches [12,31] and in all prospective probes [18,25] – some results have been negative. The inactive metabolite of the N-terminal Pro-brain natriuretic peptide (NT-proBNP) is a biomarker of the cardiac stress associated to the ventricular dysfunction and the congestive heart failure. In the study ET2DS, it was found a certain association between a greater initial value of NTproBNP and a decrease in the cognitive ability, the cognitive decline being abrupt in the older persons [25].

Peripheral artery disease and the ankle-brachial pressure index

In the persons with type 2 diabetes mellitus, the pressure index diminished at the ankle (ABI) – a measure of the peripheral artery disease (PAD) of the inferior limbs – and the generalized atherosclerosis have been correlated with a diminished cognitive function [7,25] and with dementia [12]. In Fremantle Diabetes study, 38% of the individuals without cognitive decline, 45% of the persons with decreased cognitive

functions and 75% of the persons with dementia have been associated with the presence of peripheral artery disease [12].

Overall, the proofs for an association with the macrovascular disease and the neurocognitive disorders in diabetes are unsubstantial and fluctuate depending on the vascularization area taken into consideration. As we expected, the proofs for a relation between the cerebrovascular disease particularly the stroke – are stronger than the ones for the vascular situses which are farther from the brain, including from the heart. The proofs for an association with the most distanced presentations of the macrovascular diseases are mainly limited and could reflect the atherosclerosis on a large scale as a marker for the cognitive disorders in the case of persons with type 2 diabetes mellitus, thus implying that any real associations have a small measure in the effect [31].

Depression and the pre-morbid cognitive decline

Depression

Depression is one of the most frequently mental disorders in patients with cerebral affections. In the case of certain patients, the cognitive decline could be the direct result of depression. In the case of others, the neurologic comorbid affection and depression could bring their own contribution to the cognitive profile. Another hypothesis needing to be taken into account is the one that the presence of depression can determine secondary issues as regards testing, but which doesn't necessarily reflect a subjacent cognitive deficiency [36]. In a transversal analysis of ACCORDMIND, the patients with depression (based on the score obtained on different scales, on screening or self-reporting) have also registered small scores from the neurocognitive point of view (less at the more detailed neuropsychological tests) in comparison with the patients without depression [11]. The persons with comorbid diabetes mellitus and depression obtained reduced results in the attention and working speed tests, in comparison with the patients with diabetes mellitus, but without depression [23]. In the general population, the association of depression with the cognitive deficiency seems to be well established [20]; therefore, it is possible for the depression to contribute in the promotion of cognitive deficiency associated with diabetes.

At the present day, it is not known if depression represents an independent risk factor for dementia, acting through hypercortisolism, which harms the hippocampus area, or a prodrome of dementia through the perturbation of serotoninergic circuits caused by the overall neurodegenerative process, or through psychological mechanisms linked to the inner struggle of the patient in his/her attempt to deal with the more diminished cognitive abilities [34].

Neuropathology effects

The neuropathologic features of the cerebrovascular disease (multiple heart failures) and Alzheimer's (the beta-amyloid plaques and tau protein which contribute to the neurofibrillary tangles) [16] are well established.

It is not difficult to think out the way in which the macrovascular risk factors in diabetes mellitus would contribute to the cerebrovascular affectation [9], whereas the chronic hyperglycemia can lead to the aggregation of final glycation products [8] and in the development of certain ischemic modifications in the small vessels. The hyperglycemia's neurotoxic effects are also well accepted [9] and there are firm connections between insulin and beta-amyloid protein: the insulin seems to initiate the production of beta amyloid and to

encourage its accumulation through the enzyme's degradation [32].

The neuropathologic bases of the increased risk of cognitive disorders which the persons with diabetes mellitus are exposed to are far from being singular or simple. This complexity is explained by the difficulty in developing certain efficient strategies to prevent the cognitive disorders in the persons with diabetes mellitus and in developing the treatment advances in the patients having already suffered cognitive disorders [31].

Conclusions

The majority of the studies approaching the risk factors correlated with cognitive disorders have investigated the general populations. Nevertheless, having in view the higher risk of cognitive disorders affecting patients with T2DM and the potential distinctions in the underlying mechanisms between the persons with T2DM and the regular population, it is necessary to obtain more information specific to the diabetic population. The proofs that the risk factors arise more frequently in the persons with T2DM - associated with the cognitive dysfunction - are limited, primarily because not too many of these risk factors have been deeply researched. Likewise, many of them have been assessed by themselves.

Generally speaking, we would recommend for the physicians to attenuate the emphasis on intensive care and the rigorous control of glycaemia, in their attempt to protect the patients' cognitive behavior (mainly as regards the potentially harmful effects of hypoglycemia on knowledge). In the case of modifiable risk factors, there are necessary additional studies of good quality and on significantly extensive scale in order to determine the causality in the synergy between each main risk factor and their correlation with the cognitive deterioration. For the glycaemia control, the future studies should keep on trying to separate the double potential of benefices (diminishing the glucose level in the blood) and the effects harmful to (hypoglycemia). Likewise, there could be taken into consideration new orientations for investigating the risk factors with protection role for which the proofs have been limited in a big way to the observational studies, despite the fact that they can be modified. For example, the studies could determine the effects of anti-inflammatory drugs which are already used relatively on a large scale and have a reduced cost, in order to provide definitive proofs concerning their possible associations with the incidence of neurocognitive deterioration.

Being also given the high costs involved in the case of this disease worldwide, it is hoped that a sustained research will allow the identification of the causal risk factors which can be used in order to develop preventive interventions and can help in identifying the patients representing the risk of progressing the neurocognitive deterioration

REFERENCES

1. **Lu FP, Lin KP, Kuo HK.** Diabetes and the risk of multi-system aging phenotypes: a systematic review and meta-analysis. *PLoS One* 4(1): 4114, 2009.

2. **Cooper C, Sommerlad A, Lyketsos CG, Livingston G.** Modifiable predictors of dementia in mild cognitive impairment: a systematic review and meta-analysis. *Am J Psychiatry* 172: 323–34, 2015.

3. **Cukierman T, Gerstein HC, Williamson JD.** Cognitive decline and dementia in diabetes – systematic overview of prospective observational studies. *Diabetologia* 48(12): 2460–9, 2005.

4. **Winkler A, Dlugaj M, Weimar C, et al.** Association of diabetes mellitus and mild cognitive impairment in middle-aged men and women. *J Alzheimers Dis* 42(4): 1269–77, 2014.

5. Christman AL, Matsushita K, Gottesman RF, et al. Glycated haemoglobin and cognitive decline: the Atherosclerosis Risk in Communities (ARIC) study. *Diabetologia* 54(7): 1645-52, 2011.

6. Sato N, Morishita R. Roles of vascular and metabolic components in cognitive dysfunction of Alzheimer disease: short- and long-term modification by non-genetic risk factors. *Front Aging Neurosci* 5: 1–9, 2013.

7. Chen G, Cai L, Chen B, et al. Serum level of endogenous secretory receptor for advanced glycation end products and other factors in type 2 diabetic patients with mild cognitive impairment. *Diabetes Care* 34: 2586–90, 2011.

8. Chen RH, Jiang XZ, Zhao XH, et al. Risk factors of mild cognitive impairment in middle aged patients with type 2 diabetes: a cross-section study. *Ann Endocrinol* 73: 208–12, 2012.

9. Arbelaez AM, Hershey T. Imaging hypoglycemia's effects on the human brain. *Diabet Hypoglycemia* 3(2): 3–9, 2010.

10. van Harten B, Oosterman J, Muslimovic D, van Loon BJ, Scheltens P, Weinstein HC. Cognitive impairment and MRI correlates in the elderly patients with type 2 diabetes mellitus. *Age Ageing*. 36(2): 164–70, 2007.

11. Cukierman-Yaffe T, Gerstein HC, Williamson JD, et al. Relationship between baseline glycemic control and cognitive function in individuals with type 2 diabetes and other cardiovascular risk factors: the action to control cardiovascular risk in diabetes-memory in diabetes (ACCORD-MIND) trial. *Diabetes Care* 32(2): 221–6, 2009.

12. Bruce DG, Davis WA, Casey GP, et al. Predictors of cognitive impairment and dementia in older people with diabetes. *Diabetologia* 51(2): 241–8, 2008.

13. Rojas A, Morales MA. Advanced glycation and endothelial functions: a link towards vascular complications in diabetes. *Life Sci* 76: 715–30, 2004.

14. Umegaki H, Kawamura T, Umemura T, Kawano N. Factors associated with cognitive decline in older adults with type 2 diabetes mellitus during a 6-year observation. *Geriatr Gerontol Int* 15: 302–10, 2014.

15. Williamson JD, Launer LJ, Bryan RN, et al. Cognitive function and brain structure in persons with type 2 diabetes mellitus after intensive lowering of blood pressure and lipid levels: a randomized clinical trial. *JAMA Intern Med* 174: 324–33, 2014.

16. Götz J, Lim YA, Eckert A. Lessons from two prevalent amyloidoses - what amylin and Aβ have in common. *Front Aging Neurosci* 5: 1–10, 2013.

17. Hassing LB, Hofer SM, Nilsson SE, et al. Comorbid type 2 diabetes mellitus and hypertension exacerbates cognitive decline: evidence from a longitudinal study. *Age Ageing*. 33: 355–61, 2004.

18. Bruce DG, Davis WA, Casezy GP, et al. Predictors of cognitive decline in older individuals with diabetes. *Diabetes Care* 31: 2103–7, 2008.

19. Johnson ML, Parikh N, Kunik ME, et al. Antihypertensive drug use and the risk of dementia in patients with diabetes mellitus. *Alzheimer's Dement* 8: 437–44, 2012.

20. Katon W, Lyles CR, Parker MM, Karter AJ, Huang ES, Whitmer RA. Association of depression with increased risk of dementia in patients with type 2 diabetes: The Diabetes and Aging Study. *Arch Gen Psychiatry* 69: 410–7, 2012.

21. Lamport DJ, Lawton CL, Mansfield MW, Dye L. Impairments in glucose tolerance can have a negative impact on cognitive function: a systematic research review. *Neurosci Biobehav Rev* 33: 394–413, 2009.

22. Manschot SM, Biessels GJ, de Valk H, et al. Metabolic and vascular determinants of impaired cognitive performance and abnormalities on brain magnetic resonance imaging in patients with type 2 diabetes. *Diabetologia* 50: 2388–97, 2007.

23. Watari K, Letamendi A, Elderkin-Thompson V, et al. A crosssectional survey of depression, anxiety, and cognitive function in patients with type 2 diabetes. *Arch Clin Neuropsychol* 21: 787–96, 2006.

24. Arntzen KA, Mathiesen EB. Subclinical carotid atherosclerosis and cognitive function. *Acta Neurol Scand* 124: 18–22, 2011.

25. Feinkohl I, Keller M, Robertson CM, et al. Clinical and subclinical macrovascular disease as predictors of cognitive decline in older patients with type 2 diabetes: the Edinburgh Type 2 Diabetes Study. *Diabetes Care* 36: 2779–86, 2013.

26. Misiak B, Leszek J, Kiejna A. Metabolic syndrome, mild cognitive impairment and Alzheimer's disease - the emerging role of systemic low-grade inflammation and adiposity. *Brain Res Bull* 89: 144–9, 2012.

27. Lin CH, Sheu WH. Hypoglycaemic episodes and risk of dementia in diabetes mellitus: 7-year follow-up study. *J Intern Med* 273: 102–10, 2013.

28. Whitmer RA, Karter AJ, Yaffe K, Quesenberry CP, Selby JV. Hypoglycemic episodes and risk of dementia in older patients with type 2 diabetes. *JAMA* 301: 1565–72, 2009.

29. Feinkohl I, Aung PP, Keller M, et al. Severe hypoglycemia and cognitive decline in older people with type 2 diabetes: the Edinburgh Type 2 Diabetes Study. *Diabetes Care* 37: 507–15, 2014.

30. de Galan BE, Zoungas S, Chalmers J, et al. Cognitive function and risks of cardiovascular disease and hypoglycaemia in patients with type 2 diabetes: the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial. *Diabetologia* 52: 2328–36, 2009.

31. Feinkohl I, Price JF, Strachan MWJ, Frier BM. The impact of diabetes on cognitive decline: potential vascular, metabolic, and psychosocial risk factors. *Alzheimers Res Ther* 7(1): 46, 2015.

32. Takeda S, Sato N, Rakugi H, Morishita R. Molecular mechanisms linking diabetes mellitus and Alzheimer disease: beta-amyloid peptide, insulin signaling, and neuronal function. *Mol Biosyst* 7(6): 1822–7, 2011

33. Moyer MV. Perspectives: It's not dementia, it's your heart medication - Why cholesterol drugs might affect memory, *Scientific American Mind*, 2010.

34. Henderson SA, Jorm FA. Definition and Epidemiology of Dementia: A Review. In: *Dementia, Volume 3, Second edition*, John Wiley & Sons Ltd, pp: 1-68, 2002

35. Cairns NJ. Neuroanatomy and neuropathology. In *Clinical Neuropsychology, a practical guide to assessment and management for clinicians* Goldstein LH; McNeil JE, pp 23-60, 2004.

36. Brown R. Psychological and psychiatric aspects of brain disorder: nature, assessment and implications for clinical neuropsychology. In: *Clinical Neuropsychology, a practical guide to assessment and management for clinicians*, Goldstein LH; McNeil JE, pp 81-98, 2004.

37. Norris PM, MacNeill SE, Haines ME. Psychological and neuropsychological aspects of vascular and mixed dementia. In: *Handbook of dementia. Psychological, Neurological and Psychiatric Perspectives.* Lichtenberg PA, Murman DL, Mellow AM, pp 173-196. 2003.