

COGNITIVE AND/OR DEPRESSIVE DISORDERS IN THE ELDERLY WITH TYPE II DIABETES MELLITUS ASSOCIATED WITH HYPERTENSION

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ABSTRACT

Type 2 diabetes mellitus is a significant public health problem due to its increasing prevalence, being considered a major risk factor for cardiovascular diseases, thus being an important cause of morbidity and mortality globally. NICE (The UK's National Institute for Excellence in Health and Care) states that people diagnosed with diabetes (both type 1 and type DZ 2) have a three times higher risk of being diagnosed with depression compared to those who do not have diabetes. Studies on the association of diabetes mellitus in the elderly and neurocognitive disorders have highlighted the increased incidence of dementia in this type of patient, the latter representing a risk factor for the development of strokes. The purpose of the study: to study the presence of neurocognitive dysfunction and the presence of depression in patients who simultaneously present type 2 diabetes mellitus and hypertension, and the correlations between clinical-psychiatric indicators (MMSE score and GDS-15 score) and paraclinical indicators (blood glucose level, HbA1c, total cholesterol, triglycerides, HDL- and LDL-cholesterol), as well as blood pressure values at admission, during hospitalization and at discharge. 120 patients with type 2 diabetes mellitus and HTA were examined, who followed the treatment at the National Institute of Geriatrics and Gerontology "Ana Aslan" in Bucharest, registered between April 2021 and April 2022.

Conclusions: According to the data exposed, it can be stated that there is a high probability of the development of cerebral suffering, which can generate cognitive decline of various stages of severity, in decompensated diabetic patients.

Keywords: depressive, diabetes mellitus, cardiovascular diseases

Introduction

Type 2 diabetes mellitus is a significant public health problem due to its increasing prevalence, being considered a major risk factor for cardiovascular diseases, thus being an important cause of morbidity and mortality globally. Modern medicine began to pay increased attention to improving the quality of life in pathologies with chronic evolution, given the aging tendency of the population in recent decades (1-3).

The classification of diabetes mellitus is made based on pathological processes that cause hyperglycemia. While type I diabetes mellitus is

defined by insulin deficiency and the tendency to develop ketosis, type II diabetes mellitus is a heterogeneous group of conditions characterized by varying degrees of insulin resistance, impaired insulin secretion as well as excessive production of glucose in the liver. Apart from these, there are also gestational diabetes mellitus and other specific types, which generally account for a smaller number of cases (4).

NICE (The National Institute for Health and Care Excellence UK) states that people diagnosed with diabetes (both type 1 and DZ type 2) have a three times higher risk of being diagnosed with depression compared to those who do not have diabetes (5).

Diabetes began to be responsible for the increased incidence of mortality and morbidity worldwide, according to the International Diabetes Federation (IDF): “Diabetes is one of the major health emergencies of the twenty-first century around the world. Depression in patients with diabetes mellitus aggravates the prognosis of this chronic pathology, leads to an increased risk of omission of drug treatment, and causes the quality of life to decrease, increasing mortality. (3-5)

Worldwide, according to the WHO, there are currently 425 million diabetic people; in 2045, it is expected that there will be 629. The number was estimated by applying the estimated prevalence in the Atlas „IDF diabetes” to the number of people aged 20-79 years estimated by the United Nations Population Division. The estimate includes both diagnosed and undiagnosed diabetes (6-9).

Romania is part of the 47 EU countries and a member of the IDF. The PREDATORR study “Prevalence of diabetes mellitus and prediabetes in the adult Romanian population” demonstrates the rise of cases of patients diagnosed with diabetes mellitus in the territory of our country, 70% is found in people over 60 years of age, predominantly women, compared to the male population (10, 11).

Huang CJ’s study, from, 2011, demonstrated that anxiety is much higher among patients with diabetes than among patients without diabetes (8, 12, 13). It is known the negative impact that diabetes has on all organs, including the nervous system, which most often leads to essential neuropsychic disability. Studies on the association of diabetes mellitus in the elderly and neurocognitive disorders have revealed the increased incidence of dementia in this type of patient, the latter representing a risk factor for the development of strokes, thus contributing to higher mortality compared to the elderly without cognitive dysfunction (3, 14, 15).

Research in recent years demonstrates the connection between diabetes and neuropsychiatric conditions (4, 16, 17).

Regarding the daily treatment of this category of patients, any kind of mistake or omission may favor the appearance of hypo

or hyperglycemia or the appearance of acute complications such as ketoacidosis, hyperosmolar hyperglycaemic state, hypoglycaemic coma (16, 18, 19).

In this study, we addressed known patients with diabetes who have depression or neurocognitive disorders at the same time. Cognitive alteration means an abnormal dysfunction of the cognitive function classified and evaluated based on the mental status assessment tests performed on the patient, dementia represents the most severe form of impairment, having an impact on the patient’s daily lifestyle (3, 4, 15, 20). Cognitive disorders are divided into mild, moderate, or serious. In the case of people with type 1 diabetes mellitus, neurocognitive disorders occur in terms of attention and flexibility of mental functioning and information processing, and in those with type 2 diabetes mellitus, disorders occur in terms of executive function, memory or slowing down of psychomotor reactions (6, 21). Thus, in patients who have type II diabetes mellitus, the inability to maintain their balance or slowness in movements is highlighted, grounded reasons to increase the risk of falls resulting in various traumas, especially in the elderly (21, 22). In this category of patients, it is desired that the treatment be based on simple and effective therapeutic schemes, taking into account the avoidance as much as possible of acute complications and the administration of medication with a low risk of hypoglycemia. According to recent guidelines, in diabetic elderly patients, it is recommended to implement screening for the detection of neurocognitive disorders, especially in patients over 65 years of age, taking into account the increased prevalence of cognitive dysfunction with aging.

Neuropsychological research methods are aimed at analyzing the clinical features of cognitive impairment, being represented by a series of tests that emphasize the memorization and rendering of words; image recognition representing graphic analysis; solving intellectual problems, and studying movements (8). In order to carry out this research in the field, there are a series of validated tests, such as MMSE (Mini-Mental State Examination), MoCA (Montreal Cognitive Assessment), and Geriatric Depression

Evaluation Scale (GDS-15). It is considered that the time interval at which the screening should be performed should be adapted according to the individual risk of the patient to develop the neurocognitive disorder (9). The duration of diabetes and hyperglycemia are closely related to the degree of disorders of cognitive functions, hyperglycemia having a direct impact on the activation of the polyol pathway, the triggering of protein kinase „C”, the formation of the products of advanced glycosylation, the increase of oxidative stress with the formation of free radicals, the processes of inflammation with the release of cytokines and the activation of growth factors, the activation of thrombogenesis processes, representing important aspects in the development of chronic complications micro-and macrovascular. Other factors that demonstrate the close relationship between diabetes and cognitive disorders are dyslipidemia, the action of insulin and the phenomenon of insulin resistance, and the presence of micro-and macrovascular complications. The way insulin enters the brain is through the blood-brain barrier, where it binds with insulin receptors in different brain structures, which ensures the proper running of cognitive functions. The largest number of receptors for insulin is located in the hippocampus and the cerebral cortex, these being structures involved in memory processes. Memory disorders in people who have insulin resistance and metabolic syndrome can be explained by reducing the number of receptors and decreasing their affinity to insulin. At the same time, it is considered that hypertension contributes to the development of a hereditary predisposition to a degenerative pathology such as Alzheimer's disease (23). HTA induces periodic or chronic cerebral ischemia that causes hypoxia, so in patients who present HTA, with onset symptoms of Alzheimer's disease, the appearance of a stroke causes depression of cognitive functions and the clinical manifestation of dementia (24, 25). It has been shown that there is a correlation between cognitive disorders in elderly patients with diabetes mellitus and the advanced stages of diabetic retinopathy and nephropathy, coming from impaired microcirculation, including at the cerebral level, these vessels having embryological origin and similar structure to retinal vessels.

The role of microcirculation in the occurrence of dementia is argued by the direct correlation between changes in cerebral MRI examination (leukoaraiosis, lacunar ictus, microhemorrhages, cerebral atrophy, etc.) and cognitive dysfunction. There are also correlations between depression and diabetes mellitus, depression-generating hypercortisolemia that causes the activation of pro-inflammatory reactions with stimulation of the glutamatergic system and neurodegenerative processes (apoptosis and neuronal necrosis), thus generating dementia (14, 26, 27).

The study aimed to analyze the presence of neurocognitive dysfunction or its absence and the presence of depression in patients who were simultaneously diagnosed with type 2 diabetes mellitus and hypertension and the correlations between clinical-psychiatric indicators (MMSE score and GDS-15 score) and paraclinical indicators (blood glucose level, HbA1c, total cholesterol, triglycerides, HDL- and LDL-cholesterol) as well as the tension values at admission, during hospitalization and discharge.

Material and methods

This research was based on the preparation of an observational and retrospective clinical study. To improve the level of knowledge on the topic addressed, we used research methods based on the evidence of the clinical observation sheets, the records in question, and the information system within the hospital. All patients registered in the database of the National Institute of Geriatrics and Gerontology „Ana Aslan” in Bucharest were considered valid for the study; the study was conducted on 120 patients, randomly selected. During the study, ethics issues were observed, ensuring the protection of personal data, the patients were included only numerically in the study. There were examined 120 patients with type 2 diabetes mellitus and HTA, who followed treatment at the National Institute of Geriatrics and Gerontology „Ana Aslan” in Bucharest, recorded between April 2021 and April 2022. I have taken into account the following variables: the age of the subjects (50-65 years, >70 years), the sex of the patient (male/female), the background (rural/urban), the antihypertensive treatment followed, and the duration of its administration, the

treatment of diabetes mellitus and the duration of its administration, the glycaemic values during hospitalization, the development of micro-and macrovascular complications, the association of other comorbidities, the compliance to the proposed therapy, the association of mood disorders and/or neurocognitive disorders and the frequency of clinical-biological re-evaluations (9). Clinical and paraclinical evaluations were made to assess the stage of diabetes mellitus, associated pathologies, and chronic complications. The level of cognitive dysfunction was quantified by the MMSE – Mini-Mental State Examination. The objectives and methodology of the study were approved by the Ethics and Research Commission of the National Institute of Geriatrics and Gerontology „Ana Aslan” Bucharest (28).

Results and discussions

The study group included 120 patients with type 2 diabetes mellitus and HTA associated with the age of 50-80 years, of which 73 were women and 47 men. 23 of the patients are known to have diabetes mellitus for < 5 years, 68 patients have diabetes mellitus with an age between 5-10 years, and the remaining 29 have had type 2 diabetes mellitus for over 10 years. The anthropometric data of the patients detected an average body weight of 84.82 ± 21.5 kg with an average BMI value of 35.48 ± 6.59 kg/m² were taken into account. To determine the degree of compensation of carbohydrate metabolism, the average values of blood glucose and HbA1c were calculated. The average blood glucose value was 10.17 ± 4.12 mmol/l, and HbA1c $7.46 \pm 1.75\%$. In the subjects under analysis, the values of the lipid spectrum were also taken into account. Therefore, the average value of total cholesterol was 6.24 ± 1.05 mmol/l, triglycerides 1.98 ± 0.86 mmol/l, HDL cholesterol 1.18 ± 0.34 mmol/l, LDL-cholesterol of 5.08 ± 0.89 mmol/l. Analyzing the tension values in the admitted elderly patients, there was a net majority distribution of severe HTA. It was also found that most patients over 70 years of age were undergoing antihypertensive treatment with a single drug (IECA or ARB's), a small part of them having drug combinations, compared to patients aged 50-65 years who were

undergoing treatment with drug combinations. The predominant duration of the antihypertensive treatment in the elderly was represented by 10-20 years and in terms of the age of diabetes treatment, the majority was the period of up to 10 years.

According to Poongothai S., Anjana R.M., Pradeepa R. et. al – Association of depression with complications of type 2 diabetes- the Chennai Urban Rural Epidemiology Study (CURES-102), a study conducted in India, revealed the increased prevalence of depression in patients diagnosed with type 2 diabetes complicated with retinopathy, neuropathy, chronic kidney disease or peripheral artery disease (9, 26). In newly diagnosed patients with diabetes mellitus, depression correlated with the presence of concomitant chronic complications, and prospectively the aggravation of depression was parallel to the evolution of chronic complications (20, 29, 30).

Considering the influence they can have on lifestyle, the evaluation of mental status, and the quantification of mood disorders, I mention the following aspects: obtaining the necessary information was achieved with the help of specialized questionnaires, attached to the observation sheets - Mini-Mental Status Assessment (MMSE) and Geriatric Scale for The Evaluation of Depression (GDS-15) (3). MMSE aims to identify possible neurocognitive disorders and the degree of neurocognitive damage, being achieved in optimal conditions for the patient. This questionnaire is based on simple questions that follow the following cognitive abilities of the patients: orientation in space, the ability to record information, attention and calculation, short-term memory, language, and visual-spatial perception of patients. Patients can achieve a maximum of 30 points on this test. Regarding the severity of cognitive impairment, it is evaluated as follows: MMSE score 27-30 (without cognitive impairment), MMSE score 20-26 (mild cognitive impairment), MMSE score 11-19 (moderate cognitive disorders), MMSE score > 10 (severe cognitive impairment). Regarding GDS-15 the subjects are subject to a set of 15 questions with simple answers -yes/no. A score higher than or at least equal to 5 points indicates depression in the category tested by patients. It was noted in elderly patients the predominance of both types

of disorders, both neurocognitive and depressive predominantly in the female sex.

According to the GDS-15 test, 40 patients have severe depression, of which it is noted the predominance of the female sex (27 patients) who recorded a GDS-15 score between 10-15 points, and 13 men have severe depression.

Both depression and diabetes mellitus are risk factors for the appearance of dementia, and if a patient presents both conditions simultaneously, their impact is greater (15). Based on the assessments of MMSE, diabetes mellitus is associated with an average cognitive decline in the middle and old age groups, but also with the acceleration of the process of developing dementia in elderly people with medium cognitive decline. Dementia associated or not with depression generates difficulties in the management of patients with type 2 diabetes mellitus (15).

The ADA (American Diabetes Association) recommends annual screening of all patients over 65 with diabetes, to detect as early as possible, the various neurocognitive disorders or dementia (31, 32).

MMSE tests demonstrated the lack of cognitive dysfunctions in 82 patients, of which 57 are female and 25 are male. The presence of cognitive dysfunction based on the help of MMSE tests was found in 38 patients, 21 female, and 17 male patients. 15 patients show moderate cognitive impairment, and 2 patients, both females show moderate dementia. These patients, in whom dementia was detected, suffered from decompensated diabetes with an evolution of more than 10 years, presenting complications such as diabetic retinopathy, diabetic nephropathy, and hypertension.

Parameters such as total cholesterol, HDL- and LDL-cholesterol, blood sugar, HbA1c, and triglycerides show positive correlations in relation to the severity of cognitive deficit. In direct relation to the adherence to medical recommendations, it was found the influence of these disorders on the patients' compliance. A large number of uncompliant patients were among those with depression or neurocognitive disorders.

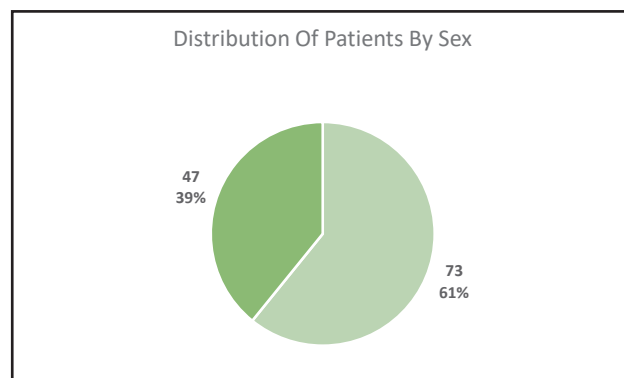


Figure 1. Distribution of patients by sex.

It is noted the predominance of female patients in the study, 73 patients out of the total of 120 registered patients. 47 patients were male.

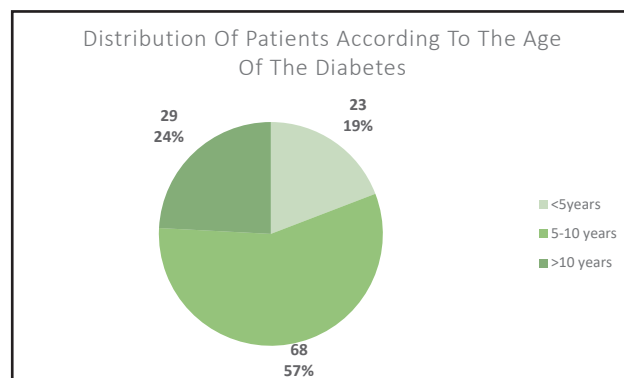


Figure 2. Distribution of patients according to the age of the DZ.

It was found that most patients, 68 have diabetes mellitus with an age between 5-10 years, 29 subjects out of the total patients have diabetes mellitus over 10 years, and 23 have diabetes mellitus with an age of fewer than 5 years.

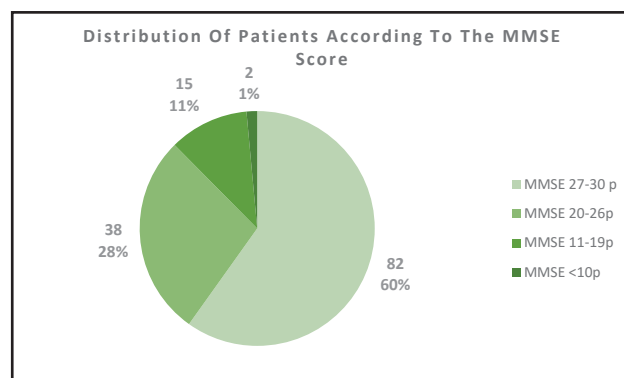


Figure 3. Distribution of patients according to the MMSE score.

There are 82 patients without cognitive dysfunction. 38 patients have mild cognitive

dysfunction, 15 patients have moderate cognitive disorders, and 2 patients have serious cognitive disorders. Glutamate is one of the neurotransmitters involved in the mechanism of cognitive disorders in diabetes, representing the main excitatory at the cerebral level. In the case of these patients with diabetes mellitus, hyperglycemia – glycosylated hemoglobin HbA1c >7% – leads to increased synthesis of glutamate and its accumulation with a neurotoxic effect, which causes the death of neurons. Normally, in the brain, glutamate is in balance with gamma-aminobutyric acid (GABA), which is an inhibitory neurotransmitter. In the case of diabetes, the ratio is modified, and neuronal apoptosis sets in, with consequences that cause cognitive decline. Impaired cognitive function in type 2 diabetes has been associated with increased diabetes duration and poor glycaemic control. On the other hand, the glycaemic peaks and postprandial hyperglycemia cause oxidative stress, involved in turn in neuronal dysfunction and, finally, in apoptosis.

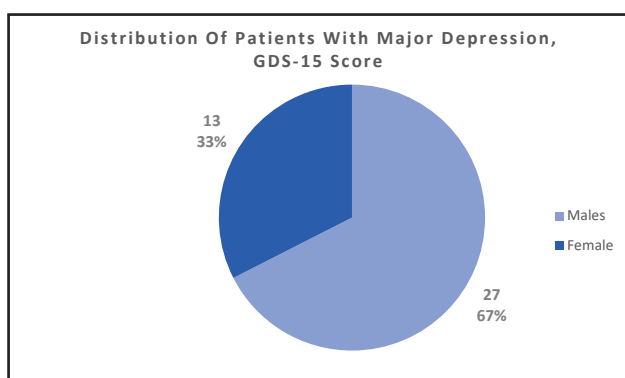


Figure 4. Distribution of patients with major depression, GDS-15 score (10-15P).

Out of the total number of patients for the study, 40 have severe depression, the female sex being the most affected, representing 27 patients. 13 male patients experienced severe depression. Neurochemical changes associated with advanced diabetes can also contribute to depression in diabetics. According to the fourth edition of the Department of Psychiatry and the Washington-based Diagnostic and Statistical Manual of Mental Illness, patients with type 2 diabetes have a prevalence of affective diseases of about 11-15% (10).

According to the literature, a study

conducted by Yatan Pal Singh Balhara in 2011 demonstrates that the greatest challenge in managing psychiatric disorders in patients suffering from diabetes is the very low rate of their detection, worrying that up to 45% of patients with psychiatric disorders remain undetected among patients treated for diabetes (12).

Conclusions

According to the analyzed data, it can be stated that there is a high probability of the development of brain suffering, which can generate cognitive decline of various stages of severity, in decompensated diabetic patients.

The idea is emerging that all patients who have diabetes mellitus, have cognitive dysfunctions of different stages, according to the MMSE test, and 40 patients present different stages of depression according to the GDS-15 test. A profile of the patient with diabetes mellitus and neuropsychiatric disorder with discernment can be achieved: female patients from an urban background, with type II diabetes mellitus, retirement, with seniority of diabetes between 5 and 10 years, or over 10 years with symptoms of depression or well-defined neurocognitive disorders.

It can be discussed the prevention of the appearance of cognitive disorders in the elderly with diabetes mellitus if the diabetes mellitus is compensated. It is necessary to know the personal risk of diabetes mellitus. The International Diabetes Federation has created an online risk assessment form – “IDF type 2 diabetes online diabetes risk assessment”. It aims to predict the individual risk of progression to type 2 diabetes over the next ten years. The test is based on the Finnish Diabetes Risk Score (FINDRISC) developed by Prof. Jaana Lindstrom and Prof. Jaakko Tuomilehto from the National Institute of Health and Well-being, Helsinki, Finland.

“Global strategy on diet, physical activity and health” complements the work of those in the field of diabetes, by focusing on population approaches to promote healthy eating and regular physical activity, thereby reducing the global problem related to obesity and overweight people.

References

1. Strachan MWJ, Reynolds RM, Frier BM, Mitchell RJ, Price JF. The relationship between type 2 diabetes and dementia. *British Medical Bulletin*. 2008;88(1):131-46.
2. Egede LE, Nietert PJ, Zheng D. Depression and all-cause and coronary heart disease mortality among adults with and without diabetes. *Diabetes Care*. 2005 Jun;28(6):1339-45.
3. Baumeister H, Hutter N, Bengel J, Härter M. Quality of life in medically ill persons with comorbid mental disorders: a systematic review and meta-analysis. *Psychother Psychosom*. 2011;80(5):275-86.
4. 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*. 2012 Apr;69(4):410-7.
5. Depression and Other Common Mental Disorders. *Global Health Estimates*. World Health Organization: 2017.
6. Ferrari AJ, Charlson FJ, Norman RE, Patten SB, Freedman G, Murray CJ, et al. Burden of depressive disorders by country, sex, age, and year: findings from the global burden of disease study 2010. *PLoS Med*. 2013 Nov;10(11):e1001547.
7. Depression. *World Health Organization*: 2021.
8. Huang CJ, Chiu HC, Lee MH, Wang SY. Prevalence and incidence of anxiety disorders in diabetic patients: a national population-based cohort study. *Gen Hosp Psychiatry*. 2011 Jan-Feb;33(1):8-15.
9. Andrus MR, Kelley KW, Murphey LM, Herndon KC. A comparison of diabetes care in rural and urban medical clinics in Alabama. *J Community Health*. 2004 Feb;29(1):29-44.
10. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care*. 2004 May;27(5):1047-53.
11. Mota M, Popa SG, Mota E, Mitrea A, Catrinoiu D, Cheta DM, et al. Prevalence of diabetes mellitus and prediabetes in the adult Romanian population: PREDATORR study. *J Diabetes*. 2016 May;8(3):336-44.
12. Balhara YP. Diabetes and psychiatric disorders. *Indian J Endocrinol Metab*. 2011 Oct;15(4):274-83.
13. Meurs M, Roest AM, Wolffenbuttel BH, Stolk RP, de Jonge P, Rosmalen JG. Association of Depressive and Anxiety Disorders With Diagnosed Versus Undiagnosed Diabetes: An Epidemiological Study of 90,686 Participants. *Psychosom Med*. 2016 Feb-Mar;78(2):233-41.
14. Holt RI, de Groot M, Golden SH. Diabetes and depression. *Curr Diab Rep*. 2014 Jun;14(6):491.
15. Dementia: supporting people with dementia and their carers in health and social care. *National Institute for Health and Care Excellence*: 2006.
16. Berge LI, Riise T, Tell GS, Iversen MM, Østbye T, Lund A, et al. Depression in persons with diabetes by age and antidiabetic treatment: a cross-sectional analysis with data from the Hordaland Health Study. *PLoS One*. 2015;10(5):e0127161.
17. Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care*. 2004 Feb;27(2):596-601.
18. Kikuchi Y, Iwase M, Fujii H, Ohkuma T, Kaizu S, Ide H, et al. Association of severe hypoglycemia with depressive symptoms in patients with type 2 diabetes: the Fukuoka Diabetes Registry. *BMJ Open Diabetes Res Care*. 2015;3(1):e000063.
19. Golden SH, Lazo M, Carnethon M, Bertoni AG, Schreiner PJ, Diez Roux AV, et al. Examining a bidirectional association between depressive symptoms and diabetes. *Jama*. 2008 Jun 18;299(23):2751-9.
20. Bartoli F, Carrà G, Crocamo C, Carretta D, La Tegola D, Tabacchi T, et al. Association between depression and neuropathy in people with type 2 diabetes: a meta-analysis. *Int J Geriatr Psychiatry*. 2016 Aug;31(8):829-36.
21. Diabetes mellitus, Nutrition, Metabolic Diseases In: Department of Diabetes NaMD, editor.: Iuliu Hatieganu University Medical Publishing House Cluj Napoca 2009. p. 28-35.

22. Romosan SL. *Medicina Longevitatii - Tratat de geriatrie* Editura Ana Aslan International Academy of Aging, Bucuresti; 2018.
23. Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011 May;7(3):270-9.
24. Nathan DM, Cleary PA, Backlund JY, Genuth SM, Lachin JM, Orchard TJ, et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med*. 2005 Dec 22;353(25):2643-53.
25. Kawamura T, Umemura T, Kanai A, Uno T, Matsumae H, Sano T, et al. The incidence and characteristics of silent cerebral infarction in elderly diabetic patients: association with serum-soluble adhesion molecules. *Diabetologia*. 1998 Aug;41(8):911-7.
26. Roy T, Lloyd CE. Epidemiology of depression and diabetes: a systematic review. *J Affect Disord*. 2012 Oct;142 Suppl:S8-21.
27. Wang X, Bao W, Liu J, Ouyang YY, Wang D, Rong S, et al. Inflammatory markers and risk of type 2 diabetes: a systematic review and meta-analysis. *Diabetes Care*. 2013 Jan;36(1):166-75.
28. Feinkohl I, Aung PP, Keller M, Robertson CM, Morling JR, McLachlan S, et al. Severe Hypoglycemia and Cognitive Decline in Older People With Type 2 Diabetes: The Edinburgh Type 2 Diabetes Study. *Diabetes Care*. 2014;37(2):507-15.
29. Poongothai S, Anjana RM, Pradeepa R, Ganesan A, Unnikrishnan R, Rema M, et al. Association of depression with complications of type 2 diabetes--the Chennai Urban Rural Epidemiology Study (CURES- 102). *J Assoc Physicians India*. 2011 Oct;59:644-8.
30. Lloyd CE, Hermanns N, Nouwen A, Pouwer F, Underwood L, Winkley K. The Epidemiology of Depression and Diabetes. *Depression and Diabetes* 2010. p. 1-27.
31. Samaan Z, Garasia S, Gerstein HC, Engert JC, Mohan V, Diaz R, et al. Lack of association between type 2 diabetes and major depression: epidemiologic and genetic evidence in a multiethnic population. *Transl Psychiatry*. 2015 Aug 11;5(8):e618.
32. Moore A, Patterson C, Lee L, Vedel I, Bergman H. Fourth Canadian Consensus Conference on the Diagnosis and Treatment of Dementia: recommendations for family physicians. *Can Fam Physician*. 2014 May;60(5):433-8.