Буковинський державний медичний університет

Міжнародний ендокринологічний журнал

Международный эндокринологический журнал

International journal of endocrinology

Mìžnarodnij endokrinologìčnij žurnal

Спеціалізований рецензований науково-практичний журнал

Заснований у вересні 2005 року

Періодичність виходу: 8 разів на рік

Том 15, № 3, 2019

Включений в наукометричні і спеціалізовані бази даних НБУ ім. В.І. Вернадського, «Україніка наукова», «Наукова періодика України», JIC index, Ulrichsweb Global Serials Directory, CrossRef, WorldCat, Google Scholar, Science Index, «КіберЛенінка», ICMJE, SHERPA/RoMEO, NLM-catalog, NLM-Locator Plus, OpenAIRE, BASE, ROAD, DOAJ, Index Copernicus

Імпакт-фактор РІНЦ: 0,227

ЗАСЛАВСКИЙ Издательский дом

journals.uran.ua

Міжнародний ендокринологічний журнал

Спеціалізований рецензований науково-практичний журнал

Том 15, № 3, 2019

DOI: 10.22141/2224-0721.15.3.2019
ISSN 2224-0721 (print)
ISSN 2307-1427 (online)

Передплатний індекс: 94553

ЗАСЛАВСКИЙ Издательский дом

Співзасновники:
Буковинський державний медичний університет,
Заславський О.Ю.

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З питань розміщення реклами та інформації про лікарські засоби:
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office@zaslavsky.kiev.ua
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Журнал внесено до переліку наукових фахових видань України, в яких можуть публікуватися результати дисертаційних робіт на здобуття наукових ступенів доктора і кандидата наук. Наказ МОН України від 15.04.2014 р. № 455.

Рекомендується до друку та до поширення через мережу Інтернет вченою радою Вищого державного навчального закладу IV рівня акредитації «Буковинський державний медичний університет» МОЗ України від 25.04.2019 р., протокол № 9.

Українською, російською та англійською мовами

Свідоцтво про державну реєстрацію друкованого засобу масової інформації КВ№19313-9113ПР. Видано Державною реєстраційною службою України 06.09.2012 р.

Формат: 60×84/8. Ум. друк. арк. 12,79
Зам. 2019-iej-99. Тираж 3 000 прим.

Адреса редакції:
а/с 74, м. Київ, 04107, Україна
Тел./факс: +38 (044) 223-27-42
E-mail: medredactor@i.ua

(Тема: До редакції «Міжнародного ендокринологічного журналу»)
http://iej.zaslavsky.com.ua

Видавець Заславський О.Ю.
Адреса для листування: а/с 74, м. Київ, 04107
Свідоцтво суб'єкта видавничої справи
ДК № 2182 від 13.05.2005 р.

Друк: ТОВ «Ландпресс»
вул. Алчевських, 2, м. Харків, 61002

International Journal of Endocrinology

Mìžnarodnij endokrinologìčnij žurnal

Specialized reviewed practical-scientific journal of endocrinology

Volume 15, № 3, 2019

DOI: 10.22141/2224-0721.15.3.2019
ISSN 2224-0721 (print)
ISSN 2307-1427 (online)

Subscription index: 94553 (in Ukraine)

ZASLAVSKY Publishing house

Co-founders:
Bukovinian State Medical University,
Zaslavsky O.Yu.

Managing Editor
Kuprinenko N.V.

Correspondence addresses:

Subscription department:
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+38 (067) 325-10-26

Advertising and Drug Promotion Department
reclama@mif-ua.com,
office@zaslavsky.kiev.ua
selezneva@mif-ua.com
v_iliyna@ukr.net

The journal is entered into the list of specific scientific publishings of Ukraine and can include doctoral and candidate thesis. Order of Ministry of Health of Ukraine dated 15/04/2014 № 455.

Recommended for publication and circulation via the Internet on the resolution of Scientific Council of State Higher Education Institution «Bukovinian State Medical University of Ministry of Health of Ukraine» (25.04.2019, Protocol № 9).

In Ukrainian, Russian and English

Registration certificate KB № 19313-9113ПР. Issued by State Registration Service of Ukraine 06/09/2012

Folio: 60×84/8. Printer's sheet 12,79
Order 2019-iej-99. Circulation 3000.

Editorial office address:
P.O.B. 74, Kyiv, Ukraine, 04107
Tel./Fax: +38 (044) 223-27-42
E-mail: medredactor@i.ua

(Subject: Editorial board of the International Journal of Endocrinology)
http://iej.zaslavsky.com.ua

Publisher Zaslavsky O.Yu.
Correspondence address: P.O.B. 74, Kyiv, 04107
Publishing entity certificate
ДК № 2182 dated 13/05/2005

Print: Landpress Ltd.
Alchevskykh str., 2, Kharkiv, 61002

International Journal of Endocrinology

Передова стаття
/Leading Article/

UDC 616.379-008.64-053.89/.9-06:616.89-008.45/.46 *DOI: 10.22141/2224-0721.15.3.2019.172103*

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Diabetes mellitus and Alzheimer's disease

For cite: Mìžnarodnij endokrinologìčnij žurnal. 2019;15(3):188-195. doi: 10.22141/2224-0721.15.3.2019.172103

Abstract. *The article reviews modern information on epidemiology and risk factors for Alzheimer's disease in diabetes mellitus. The literature data on the main pathogenetic links of the development of neurodegenerative disorders in diabetic patients, as well as the mechanisms of mutual burden are analyzed. The article deals with the results of clinical studies on the possibilities of pathogenetic correction of cognitive disorders in Alzheimer's disease, which runs on the background of diabetes mellitus.*
Keywords: *diabetes mellitus; Alzheimer's disease; cognitive disorders; review*

Increasing number of elderly people and changed age structure led to an evaluation of the number of elderly people who suffer from cognitive function disorders and dementia — a severe cognitive disorder that develops gradually and is accompanied by a decrease in cognitive activity of the brain, loss of previously acquired knowledge, the ability to take care of themselves and be responsible for their actions.

According to the World Health Organization (WHO), there are almost 50 million dementia patients in the world, about 10 million new cases are registered annually, with two-thirds of them being patients with Alzheimer's disease (AD). This is an extremely important medical and social problem due to the need for constant physical, psychological care for patients and significant economic costs. Prognosing is rather disappointing: by 2030, the number of patients expected to increase to 82 million, and by 2050 — up to 152 million [1]. High prevalence combined with enormous socio-economic significance makes dementia one of the priorities of the WHO activity.

Recently, there was convincing evidence that diabetes mellitus (DM), primarily type 2, is an independent factor for the development of cognitive impairment and is associated with an increased risk for dementia development, the main causes of which are AD and vascular dementia [2].

The results of epidemiological, visualization and autopsy studies showed the presence of both cerebrovascular and neurodegenerative mechanisms of brain lesions in the central nervous system. According to a number of large-scale prospective studies, the risk of dementia in patients with DM type 2 increases almost twice, with the risk of vascular dementia increasing by 2–2.5 times, and Alzheimer's disease — approximately 1.5 times [3, 4]. Recently, it is noted that DM type 2 is characterized by the development of mixed type dementia — vascular and Alzheimer's [5]. In addition, it has been found that type 2 DM can also affect the prevalence of moderate cognitive impairment, which is considered to be preclinical dementia. It is predicted that the increase in the number of patients with type 2 DM and aging will contribute to a further increase in these indicators [6].

In turn, the cognitive disorders in the DM impedes the patient's adaptation, adversely affects compliance, worsens the performance of medical recommendations, in particular regarding diet, oral hypoglycemic agents,

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insulin therapy, self-monitoring, etc., which makes it impossible to compensate for the disease and poses a serious threat to the occurrence of episodes of hypoglycemia and fatal consequences.

Recently, special attention of scientists is given to the connection between the DM and AD, which, as it turned out, have common mechanisms for the emergence and interconnection.

AD is the most common form of primary degenerative dementia of the late age, characterized by gradual low-grade onset, a steady progression of memory disorders and higher cortical functions up to the total collapse of intelligence and mental activity in general, as well as a characteristic complex of neuropathological symptoms. For the first time, the disease was described in 1907 by the German psychiatrist Alois Alzheimer. As a rule, it is found in people older than 65 years, but there is an early AD — a rare form of the disease. Dementia at AD with an early onset is characterized by a debut at the age of 65 years, with a more rapid course and the prevalence of aphasia-apraxia-agnosia symptoms. Early onset is more often associated with a family history of the disease. If a person suffers from this form of AD, the risk of getting sick in his children is about 50 %. Dementia at AD with a late onset runs more slowly, with predominant memory impairment. The disease occurs sporadically [7, 8].

AD frequency increases with age. So, at the age of 65–69 years, it is 3 %, 70–74 years — 6 %, 75–79 years — 9 %, 80–84 years — 23 %, 85–89 years — 40 %, over 90 years — 69 % [9].

The mechanisms that underlie cognitive dysfunction in type 2 DM have not been fully disclosed at the same time, but a number of convincing hypotheses regarding the formation of vascular, neurodegenerative and metabolic disorders have been proposed.

The factors for the development of cognitive impairment in DM include hyperthyroidism and hypoglycemia, hyperinsulinemia, cerebral insulin resistance, the formation of end-product glycation, the competition of insulin-degrading enzyme with inhibition of the degradation of β-amyloid peptides, micro- and macrovascular cerebral violations, inflammation, acute cerebrovascular abnormalities of blood circulation, etc. In the end, it is likely that the cause is multifactorial, but the leading role belongs to chronic hyperglycemia and insulin resistance [6].

Previously it was believed that glucose is consumed by the brain due to insulin, independently due to GLUT-1 and GLUT-3 transporters, and insulin signaling mechanisms are implemented mainly on the periphery. At the same time, it is finally discovered that this hormone has a neuromodulatory effect on the brain. Signaling of insulin is involved in numerous cerebral functions, including cognition and memory. It is proved that insulin directly provides glucose metabolism in the structures of the central nervous system [10].

In the brain, insulin and insulin-like growth factor (IGF) rapidly bind to tyrosine kinase receptors, IGF receptors and insulin receptors due to the high degree of identity. Insulin receptors are localized in certain parts of the brain, namely the olfactory bulb, the cerebral cortex, the hypothalamus, the tonsil, and the striate body, but their highest concentration is in the hippocampus, which is responsible for the mnemonic functions. The binding of insulin to the receptor substrate leads to its autophosphorylation, which initiates the activation of phosphatidylinositide-3-kinase, which stimulates the production of protein kinase B and inhibition of glycogen synthase-3 kinase. All this ensures membrane-stabilizing action by suppressing the production of free radicals. It is proved that insulin-stimulated glucose transport in neurons increases the activity of cholinergic synapses in the central nervous system, which creates a substrate for the implementation of higher brain functions. In turn, experimental DM in animals contributes to the reduction of neuroplasticity in the neurons of the hippocampus in the context of a violation of glutamate neurotransmission due to a decrease in the density of NMDA receptors [10–12].

Today, there is no doubt that one of the leading factors for the development of cognitive impairment in diabetes is chronic hyperglycemia, which manifestation is associated with cognitive deficits. The results of many studies in patients with DM of both types have demonstrated a close relationship between glycemia and glycated hemoglobin (HbA1c) and disorders of higher brain function. It has also been established that a higher average daily glycemia is associated with an increased risk of dementia. Negative correlation with cognitive functions also was revealed for the index of postprandial glycemia [13].

As a result of persistent hyperglycemia, processes of glucose binding to amino groups of proteins are enhanced, with the formation of heterogeneous and unstable compounds — end-product glycation, which have the ability to modify neurofibrillary tau protein tangles and beta-amyloid plaques, which obviously contributes to the progression of neurodegeneration in AD.

Therefore, according to the scientists' results, the better control of blood glucose levels is necessary to prevent the development of cognitive impairments of different origin in patients with type 2 DM [13].

On the other hand, an extremely important factor in the development and progression of cognitive disorders is hypoglycemia, because normal brain function depends directly on the level of glucose as the main source of energy for cerebral metabolism. Acute hypoglycemia, in addition to neuroglycopenic reactions, provokes cardiovascular crises and hemorheological disorders along with the activation of the sympathoadrenal system and hormonal dysregulation. At the same time, hemodynamic and hemorheological disorders that develop in the context of endothelial dysfunction, oxidative stress, violation of the cytokine link of immune regulation, activation of apoptosis factors, etc., increase the risk of local focal tissue ischemia and the manifestation of vascular events [14].

According to the experimental studies, hypoglycemia leads to necrosis of neurons in the hippocampus and

cortical regions, and repeated hypoglycemia can lead to synaptic dysfunction, even in the absence of neurons' death [15].

At the same time, the results of studies demonstrated that the relationship between the risk for developing cognitive impairment and the frequency and severity of hypoglycemic episodes are controversial. According to some data, in patients with single or multiple episodes of hypoglycemia, a proportional increase in the risk of dementia was observed [16]. Another Edinburgh Type 2 Diabetes Study has shown that both history of hypoglycemia and an incident of hypoglycemia are associated with severe cognitive disorder [17].

In turn, the disruption of cognitive function increases the risk of hypoglycemia due to poor patient compliance, dietary disorders, the overdose of hypoglycemic agents, and so on. Thus, in the ADVANCE study, severe cognitive disorder, established on the basis of MMSE test, contributed to a significant (more than double) increase in the risk of hypoglycemia [18]. It is noted that the presence of cognitive impairments prevents the timely recognition of patient hypoglycemia, the possibility of timely and adequate medical care, poses a threat to the occurrence of severe hypoglycemic episodes and various complications that threaten fatal consequences [16–18].

In patients with type 2 DM, a negative correlation between cognitive function and insulin, C-peptide and HOMA index is also established, indicating the role of insulin resistance and hyperinsulinemia in the development of cerebral disorders in this disease [19].

Studies in recent years show that cognitive dysfunction with type 2 DM on the background of AD can be related to insulin resistance of the brain, which leads to neurodegeneration, that allowed scientists to conventionally consider dementia a kind of "diabetes of the brain" or "type 3 diabetes" [20].

This hypothesis is confirmed by the fact that the level of insulin and the number of insulin receptors in AD patients, especially in the brain, related to learning and memory, are significantly higher than in healthy subjects. As already noted, insulin and its signaling pathways not only regulate the metabolism of glucose and energy but also modulate learning and memory. Since cognitive structures such as the hippocampus and the anterior cortex (part of the cerebral cortex located in the temporal lobe related to the hippocampal formation) have a high density of insulin receptors and can locally produce insulin, an obstacle in any way insulin signaling can lead to cognitive impairments, most of which is associated with memory, attention, and executive functions [21].

This is confirmed by the fact that there is a decrease in the expression of genes encoding insulin secretion signaling proteins and a lower level of several proteins in this pathway at the intersection of Alzheimer's disease. In addition, plaques that occur in AD and neurofibrillary tangles contain glycated protein, the formation of which may be provoked by the impossibility of insulin action [21–23].

Experimental studies have shown that due to insulin resistance excessive proteins activation of the signaling pathway of insulin in the brain causes the formation of amyloid plaques, which negatively affects both short-term and long-term memory, as well as cognitive function. In this case, there is a violation of the cascade reactions signaling, including inhibition of phosphatidylinositide-3-kinase, protein kinase B and activation of 3-kinase glycogen synthase, which induces hyperphosphorylation of tau protein, accumulation of oligomers and oxidative stress leading to mitochondrial dysfunction, apoptosis, secretion of proinflammatory cytokines, and neurodegeneration [22, 23].

In particular, it has been proven that insulin is involved in the regulation of protein synthesis of the precursor of amyloid APP and β-amyloid, the main component of amyloid deposits, and also regulates the phosphorylation of tau protein, which forms the basis of neurofibrillary formations. In this case, this hormone stimulates the transferring of APP-β-amyloid to the membrane and extracellular release of β-amyloid, and insulin resistance causes an increase in the activity of β- and γ-secretase, with subsequent increase in the content of β-amyloid [24, 25].

Another theory is related to the reduction in the elimination of β-amyloid, whose cerebral clearance can be implemented by microglial capture or by the insulin-degrading enzyme. However, insulin resistance competes with β-amyloid, which contributes to the accumulation of β-amyloid in the brain [29, 30]. Lowering insulin sensitivity may result in the activation of the enzyme GSK-3beta, which catalyzes the phosphorylation of tau protein, a major component of neurofibrillary tangles [26].

In recent years, the hypothesis about the role of hyperamylinemia in the development of AD has been actively discussed. Amylin (or islet amyloid polypeptide) is a neuroendocrine hormone secreted by beta cells together with insulin. By interacting with the nuclei of the brain, it regulates the sense of saturation through central mechanisms, reduces appetite, stomach emptying speed, and also suppresses glucagon secretion, preventing postprandial hyperglycemia. Today amylin is considered as the third islet pancreatic hormone (along with insulin and glucagon), which is involved in maintaining glucose homeostasis. In this case, hyperamylinemia, which is often recorded in patients with obesity and insulin resistance, leads to oligomerization of this polypeptide, an increase in its deposition in pancreatic islets, a decrease in the number of β-cells by amplifying the processes of apoptosis and/or necrosis and thereby increasing the rate of absolute insulin deficiency development. A recent study has shown that polymorphism of the amylin gene is associated with AD [27]. Independent studies have shown that elderly patients with AD or moderate cognitive impairment had lower amylin plasma concentrations than controls [28]. The brain tissue analysis of persons with AD, which runs on the background of DM, revealed the deposition of a significant amount of amylin in the gray matter and in

the walls of the brain vessels. It is noteworthy that this substance was found in the brain of patients with AD without diabetes [29]. In view of the above, an amylin analogue used as an informative and non-invasive challenge test for Alzheimer's disease [30].

Thus, hyperglycemia, activating free radical oxidation and non-enzymatic glycosylation of proteins, the polyol glucose metabolism pathway, the formation of end-product glycation, leads to endothelial dysfunction, hemorheological disorders with the development of microvascular lesions of the brain; and the presence of insulin resistance and hyperinsulinemia further contribute to the development and progression of neurodegeneration mechanisms, as well as dyslipidemia, arterial hypertension and cerebral atherosclerosis, which generally causes the development of cerebral lesions. Due to the prevailing cardiovascular, neurodegenerative and metabolic disorders, there is a gradual decrease in the gray matter of the brain, changes in its microstructure and white matter atrophy.

The results of studies have shown that in patients with type 2 DM the degree of cognitive impairment is associated not only with carbohydrate dysmetabolism but also with the presence of arterial hypertension, dyslipidemia, and acute cerebrovascular accidents. At the same time, the risk of cognitive impairment persists even in case of correction of a number of its factors, such as arterial hypertension and dyslipidemia, which may be indicative of the determining role of carbohydrate metabolism disorders (chronic hyperglycemia, insulin resistance, hyperinsulinemia, and hypoglycemia) in the development of diabetic cerebral disorders [25, 31].

Since chronic hyperglycemia plays a leading role in the development of cerebral diabetic disorders, the key to preventing the development and progression of cognitive impairment in diabetes is satisfactory glycemic control. At the same time, the advantages of maximum compensation for type 2 DM are controversial. Thus, in a number of studies, satisfactory glycemic control was associated with less pronounced cognitive impairment [32, 33]. In contrast, the ACCORD-MIND study, conducted in 52 clinical centres in North America with the involvement of about 3,000 patients with type 2 DM, has shown that active glycemic control is not associated with improved cognitive performance in patients with type 2 DM [34]. In addition, such approach may be dangerous in terms of the risk of hypoglycemic reaction, which adversely affects cognitive function [17, 18].

Taking into account all of the foregoing, the strategy for the treatment and prevention of cognitive impairment in diabetes should be individualized in such a way as to minimize the occurrence of both hyperglycemia and hypoglycemia and to be effective in the aspect of the prevention of vascular complications [35].

Currently, only a few groups of drugs are prescribed for the treatment of AD, while their effects are rather modest and pathogenetically do not impact the underlying process of the disease. Due to the close pathogenetic linkages of the diabetes mellitus development mechanisms and AD, today the issue of the antidiabetic therapy influence on the cognitive function of patients with DM is actively studied.

In some studies, both monotherapy with insulin drugs and in combination with oral hypoglycemic agents positively influence the cognitive functions in AD, which, according to the authors' data, is related to the optimization of glycemic control [36]. Individual works showed improvement in memory and other cognitive functions against the background of the intranasal insulin use in AD [37].

At the same time, several other studies have found that the use of insulin drugs, especially in the elderly people, is more often associated with deterioration of cognitive function, which is associated with an increased risk of hypoglycemia and low compliance of patients. In particular, in Rotterdam study, the patients received insulin drugs had the highest risk for dementia [4].

Therefore, during the treatment of elderly persons with cognitive impairment, it is necessary to avoid the administration of short- and short-acting insulin drugs, complex administration regimens and, as a baseline therapy, to favor low-profile insulin hypoglycemic reactions, in particular, insulin analogues.

As the results of many studies provided convincing evidence of the role of insulin resistance in the development of cognitive impairment in type 2 DM, the most promising hypoglycemic agents to prevent their development are recognized drugs from the group of insulin sensitizers.

To date, the first choice for the treatment of type 2 DM is metformin [38], which has unique pleiotropic effects that affect the main pathogenetic links in the development of cerebral diabetic lesions: chronic hyperglycemia, insulin resistance, hyperinsulinemia, hyperlipidemia, inflammation of the vascular walls and endothelial dysfunction, oxidative stress, disturbances of the rheological properties of blood, prevents the development of GTPM and has a high safety spectrum related to the occurrence of hypoglycemic reactions.

The results of recent studies have shown that, besides the listed mechanisms, metformin possesses a whole spectrum of neurospecific properties that generally prevent the progression of diabetic cerebral abnormalities and provide a nootropic effect. First of all, the neuroprotective activity of metformin is indicated, which is ensured by activation of AMPK-dependent pathways in human nervous stem cells, which causes angiogenesis, neurogenesis, and induction of autophagy [38]. It is proved that the increase in neurotrophic factors in the brain is observed against the background of the drug application, and the intensity of neurogenesis in the hippocampus increases twice [39, 40]. The results of experimental studies have shown that metformin reduces neurocytes apoptosis [41]. There is also evidence that the use of metformin prevents the brain mitochondrial dysfunction [42]. The studies of recent years have shown that this drug effectively inhibits the formation of beta-amyloid and prevents the development and progression of AD. It has been shown that the metformin

use background revealed a significant deterioration in the expression and β-secretase activity, leading to the formation of Aβ (β-amyloid) [43, 44]. Metformin ability to reduce the activity of acetylcholinesterase deserves particular attention.

According to clinical observations, metformin is associated with a decrease in the dementia frequency and cognitive function improvement in elderly patients with DM. In a large-scale study conducted in the United States, the use of metformin in the elderly suffering from diabetes (up to 6,000 patients included in the analysis), the risk of development of neurodegenerative diseases, including AD, did not undergo statistically significant changes 1 year after the onset, the difference in 2 years decreased by 29 %, in the period from 2 to 4 years — by 41 %, and when applied more than 4 years — by 84 % compared with non-recipients [46].

It is noteworthy that the established effectiveness of metformin use at AD in people without diabetes, which turned out to be safe, was associated with improvement in executive functions, in learning, memory, and attention [47].

However, in some studies, with the use of metformin, an increase in the incidence of cognitive impairment was observed in patients with vitamin B_{12} deficiency [48, 49]. The administration of a prolonged form of the drug ensures minimizing the risk of developing vitamin B_{12} deficiency against the background of metformin use due to its absorption throughout the intestine without blocking the vitamin B_{12} receptors in the ileum [50].

Hopes on the promising use of thiazolidinediones to treat and prevent cognitive impairment have not found convincing clinical evidence. In a number of studies, even deterioration of cognitive function was observed on the background of thiazolidinediones use. In particular, in the ACCORD-MIND cohort, the effect of rosiglitazone was associated with a greater reduction in cognitive performance than insulin therapy [51]. According to another large-scale study, the risk of dementia increased by more than 5-fold in patients receiving thiazolidinediones compared to those receiving metformin [52].

The results of the most studies indicate a negative effect of sulfonylureas on cognitive function, which is associated with a higher incidence of hypoglycemic responses in the context of receiving these drugs.

It has been found that the risk of severe hypoglycemia in the elderly who receive the drugs of this group, in particular glibenclamide, is significantly higher than that of young adults, as sensitivity to them may increase, especially in individuals over the age of 80, which exacerbates cognitive impairment [53].

During another retrospective cohort study, it was found that in rigidly controlled (HbA1c < 7 %) patients with type 2 DM and dementia aged ≥ 65 years, the vast majority of whom received sulfonylureas and/or insulin, there was a much higher risk of hypoglycemia, which, according to researchers' data, led to the progression of dementia. With this in mind, researchers point out the need to revise therapy with the patients transfer to other hypoglycemic agents [54].

Recently, there were papers devoted to the study of the efficiency of incretin modulators in preserving cognitive functions.

According to experimental studies data, glucagon-like peptide-1 (GLP-1) and its analogues crossing the blood-brain barrier exhibit the ability to mediate many neuronal functions by improving neurogenesis, reducing apoptosis, protecting neurons from oxidative stress, and reducing the formation of amyloid plaques, which has a positive effect on cognitive functions [57–60]. It was shown that GLP-1 agonists decrease the level of α-amyloid oligomers and toxicity in cultured primary neurons and neuronal cell lines [56, 57]. However, other works do not record the impact of GLP-1 analogues long-term use on amyloid plaques [58].

Similar effects were also observed for inhibitors of dipeptidyl peptidase-4. In experimental animal studies, the drugs of this group revealed neuroprotective properties in both AD and in vascular dementia due to the amyloid plaques formation reduction, activation of neurogenesis, antiapoptotic and antioxidant properties [59, 60].

Also, the effect of SGLT2 inhibitors on cognitive function is studied today. It has been shown that the use of SGLT2 inhibitor empagliflozin in experimental DM type 2 in mice resulted in a decrease in the manifestations of cognitive dysfunction caused by additional irradiation of the brain, which, according to the authors' data, is associated with positive cardiovascular effects of the drug [61]. It has also been found that SGLT2 inhibitors, in particular, dapagliflozin and canagliflozin, have anticholinesterase activity in experimental animals and therefore potentially improve cognitive function [62, 63].

One of the most promising antidiabetic agents that can be effective in the treatment and prophylaxis of AD in diabetes are amylinomimetics, in particular, pramlintide — a synthetic analogue of amylin. Recent studies have shown that the use of amylin and pramlintide positively affects the main pathological components of AD, in particular, amyloid plaques, tauopathy, neuroinflammation and other cerebral mechanisms, which were accompanied by improvements in training and memory rates in experimental models. Today amylinomimetics are considered as the only new therapeutic agents for targeting multiple indices of neurodegeneration in the brain in AD [30, 64, 65].

Today, the question of the effectiveness of incretin modulators, SGLT2 inhibitors, and amylinomimetics needs further study in experimental and clinical researches.

Thus, the results of numerous studies indicate an increase in the rate of development of AD in diabetes, the existence of close mechanisms of development and the inner convergence of these diseases, indicating the need to find new diagnostic methods and common pathogenetic treatment.

Conflicts of interests. Authors declare the absence of any conflicts of interests that might be construed to influence the results or interpretation of their manuscript.

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Received 07.04.2019

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Цукровий діабет і хвороба Альцгеймера

Резюме. В оглядовій статті наведені сучасні відомості щодо епідеміології та чинників ризику розвитку хвороби Альцгеймера при цукровому діабеті. Проаналізовано дані літератури щодо основних патогенетичних ланок розвитку нейродегенеративних порушень у пацієнтів із цукровим діабетом, а також механізмів взаємообтяження. Наведені результати клінічних та експериментальних досліджень щодо можливостей патогенетичної корекції когнітивних порушень при хворобі Альцгеймера, яка перебігає на тлі цукрового діабету, зазначені найбільш перспективні напрямки наукових досліджень із цієї проблеми.

Ключові слова: цукровий діабет; хвороба Альцгеймера; когнітивні порушення; огляд

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Сахарный диабет и болезнь Альцгеймера

Резюме. В обзорной статье приведены современные сведения об эпидемиологии и факторах риска развития болезни Альцгеймера при сахарном диабете. Проанализированы данные литературы по основным патогенетическим звеньям развития нейродегенеративных нарушений у пациентов с сахарным диабетом, а также механизмам взаимоотягощения. Представлены результаты клинических и экспериментальных исследований относительно возможностей патогенетической коррекции когнитивных нарушений при болезни Альцгеймера, которая протекает на фоне сахарного диабета, указаны наиболее перспективные направления научных исследований по данной проблеме.

Ключевые слова: сахарный диабет; болезнь Альцгеймера; когнитивные нарушения; обзор