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## Obesity and Alzheimer's disease

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**Abstract.** *The article reviews modern information on epidemiology and risk factors for Alzheimer's disease in obesity. The literature data on the main pathogenetic links of the development of neurodegenerative disorders in patients with obesity and metabolic syndrome are analyzed, as well as the mechanisms of mutual burden. 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 obesity.*

**Keywords:** *obesity; metabolic syndrome; Alzheimer's disease; cognitive disorders*

The prevalence of obesity has increased worldwide during the past 50 years, reaching pandemic levels. Today, the number of people suffering from obesity in the world has already exceeded 2 billion, that is about 30 % of the total population (in Ukraine, for example, — 24 %, in the Czech Republic — 26 %, in the United Kingdom — 28 %, in the USA — 36 %). More than 3 million people die each year as a result of being overweight or obese [1]. This situation is a consequence of an increased hypodynamic lifestyle through urbanization and technological advancement, excessive calorie intake, and longer life expectancy for our planet's inhabitants.

Obesity is a global problem of mankind because it significantly increases the risk of serious diseases such as type 2 diabetes mellitus (DM), fatty liver disease, hypertension, myocardial infarction, stroke, depression, osteoarthritis, Pickwickian syndrome, obstructive sleep apnoea, several types of cancer etc., thereby contributing to a decline in both quality of life and life expectancy. Obesity is also associated with increased spending on health and with such socio-economic problems as unemployment, social disadvantages and reduced economic productivity [2, 3].

On the other hand, population aging has led to an increase in the number of people with cognitive impairment, in particular with dementia, that is an extremely important medical and social problem due to considerable economic costs and a requirement for constant physical, psychological care for these patients. According to the World Health Organization (WHO), there are almost 50 million patients with dementia in the world, about 10 million new cases are registered annually, with two-thirds of them being patients with Alzheimer's disease (AD). Currently, the estimated proportion of the general population aged 60 years with dementia is 5–8 %. The future prognosis is rather disappointing: by 2030, the number of patients is expected to increase to 82 million, and by 2050 — up to 152 million [4]. Most of this increase is explained by the growth in the number of people with dementia living in low- and middle-income countries. High prevalence combined with enormous socio-economic significance makes dementia one of the priorities of the WHO.

It is known that approximately 70 % of the risk of developing AD is caused by genetics. However, there is increasing evidence that such factors as cerebrovascular disease, DM, hypertension, obesity, and dyslipidemia increase the risk of developing AD [5].

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The issue of obesity and Alzheimer's remains one of the most debatable. Despite the discovery of a large number of pathogenetic mechanisms, the causality of these pathological conditions has not yet been fully established. It should also be noted that the existing data on this issue are extremely contradictory and sometimes radically opposite.

The results of many experimental and clinical studies give reasons to consider obesity one of the risk factors associated with AD. In particular, an increase in fat content in the diet of mice was accompanied by an increase in amyloid- $\beta$  (A $\beta$ ) accumulation in the hippocampus and cognitive dysfunction [6–8]. In clinical studies, the degree of cerebral atrophy according to neuroimaging in individuals with moderate cognitive impairment is associated with an increase in body mass index (BMI) [9].

Many researchers point to the higher prevalence of obesity and overweight in AD. In particular, in the population study, overweight and obesity in middle age were associated with dementia with odds ratio of 1.71 and 3.88, respectively [10].

According to a meta-analysis of L.A. Profenno et al. [11], obesity is significantly and independently associated with the high risk of developing AD. Moreover, the results of D. Gustafson et al. [12] showed that in women of 70 years of age, every 1.0 increase in BMI is accompanied by a 36% increase in AD risk. Another study showed an association of high risk of developing AD and waist-to-hip ratio [13].

However, as other studies have shown, the risk of obesity-related dementia is gradually diminishing with age [14, 15]. According to the data of Whitehall II Study [16], obesity (BMI  $\geq 30$  kg/m<sup>2</sup>) at the age of 50 years (hazard ratio (HR) = 1.93; 1.35–2.75) but not at 60 or 70 years was associated with risk of dementia. The meta-analysis performed by Fitzpatrick et al. [17] indicated that in later stages of life obesity inversely correlated with the risk of dementia (HR: 0.63; 95% confidence interval (CI): 0.44–0.91). The same authors also reported that below ideal weight (BMI < 20 kg/m<sup>2</sup>) is also associated with an increased risk of dementia (HR: 1.62, 95% CI: 1.02–2.64). Another meta-analysis by Anstey et al. [18] indicated that both low weight and overweight, as well as obesity at middle age, are associated with a higher risk of dementia development.

Of particular note is the recent meta-analysis of the association of change in body weight with risk of dementia and its subtypes, involving 2.8 million adults with 57,294 dementia cases [19]. According to the results of this analysis, compared with body mass index defined lower-normal weight (18.5–22.4 kg/m<sup>2</sup>), the risk of all-cause dementia was higher among underweight individuals but lower among those with upper-normal (22.5–24.9 kg/m<sup>2</sup>) levels. Obesity was associated with higher risk in vascular dementia. Similarly, relative to the lowest fifth of waist circumference, those in the highest fifth had nonsignificant higher vascular dementia risk. Weight loss was associated with higher all-cause dementia risk relative to weight maintenance. Weight gain was weakly associated with higher vascular dementia risk. The relationship between body size, weight change, and dementia is complex and exhibits non-linear associations depending on dementia subtype under scrutiny.

Thus, obesity is an independent risk factor for the development of AD, at least in middle-aged people.

According to most scientists, the development of dementia is caused not so much by obesity itself, but by its metabolic complications — DM, hypertension, dyslipidemia and other components of the metabolic syndrome (MS) [20–23]. The pathogenesis of dementia in MS is multifactorial, including both vascular damage and non-ischemic neuronal death through neurodegeneration. Neurodegenerative and ischemic lesions do not simply coexist in the brain through independent evolution, but rather exacerbate each other, leading to more severe consequences for cognition than any pathology itself. In addition to the universal mechanisms of cognitive dysfunction shared by all components of MS, other pathogenetic pathways also lead to cognitive deficits and dementias that are specific to each component.

As we indicated before, 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 [24]. According to a number of large-scale prospective studies, the risk of dementia in patients with type 2 DM increases almost twice, with the risk of Alzheimer's disease — approximately 1.5 times [25, 26]. Recently, it is noted that type 2 DM is characterized by the development of mixed type dementia — vascular and Alzheimer's [27]. It has been found that type 2 DM can also affect the prevalence of mild cognitive impairment, which is considered to be pre-clinical dementia. It is predicted that an increase in the number of patients with type 2 DM and aging will contribute to a further increase in these indicators [28].

The mechanisms that underlie cognitive dysfunction in type 2 DM have not been fully disclosed yet, but a number of convincing hypotheses regarding the formation of vascular, neurodegenerative and metabolic disorders have been proposed. The factors of the development of cognitive impairment in DM include hyper- and hypoglycemia, hyperinsulinemia, cerebral insulin resistance, the formation of glycation end-products, the competition of insulin-degrading enzyme with inhibition of the degradation of  $\beta$ -amyloid peptides, micro- and macrovascular cerebral violations, inflammation, acute cerebrovascular accidents, etc. In the end, the cause is likely multifactorial, but the leading role belongs to chronic hyperglycemia and insulin resistance [22, 28–32].

Previously, it was thought that glucose is consumed by the insulin in the brain, independently due to GLUT-1 and GLUT-3 transporters and insulin signaling mechanisms are realized 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 proven that insulin directly provides glucose metabolism in the structures of the central nervous system [23, 28, 29].

Insulin and insulin-like growth factor rapidly bind to tyrosine kinase receptors in the brain, insulin-like growth factor 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 striped 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 phosphatidylinositol-3-kinase, which stimulates the production of protein kinase B and inhibition of glycogen synthase kinase-3. All this ensures membrane-stabilizing action by suppressing the production of free radicals. It is proven that insulin-stimulated glucose transport in neurons increases the activity of cholinergic synapses in the central nervous system, which creates a substrate for the realization 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 N-methyl-D-aspartate receptors [28–30].

In patients with type 2 DM, a negative correlation is also found between cognitive function and insulin, C-peptide and the homeostatic model assessment, indicating the role of insulin resistance and hyperinsulinemia in the development of cerebral disorders in this disease [31].

Studies in recent years show that cognitive dysfunction can be related to *insulin resistance* and *neuroinflammation* 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” [32].

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 part 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 produce insulin locally, an obstacle at any point of insulin signaling can lead to cognitive impairment, most of which is associated with memory, attention, and executive functions [23, 33].

This is confirmed by the fact that the autopsy of people died of Alzheimer’s disease has shown a decrease in the expression of genes encoding insulin secretion signaling proteins and a lower level of several proteins in this pathway. 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 [23, 33–35].

Experimental studies have shown that due to insulin resistance, excessive protein activation of the insulin signaling pathway 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 signaling cascade, including inhibition of phosphatidylinositol-3 kinase, protein kinase B and activation of glycogen synthase kinase-3, which induces hyperphosphorylation of tau protein, accumulation of oligomers and oxidative stress leading to mitochondrial dysfunction, apoptosis, secretion of proinflammatory cytokines, and neurodegeneration [34, 35].

In particular, it has been proven that insulin is involved in the regulation of synthesis of amyloid precursor protein (APP) and  $\beta$ -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 transfer of APP and  $\beta$ -amyloid to the membrane and extracellular release of  $\beta$ -amyloid, and insulin resistance causes an increase in the activity of the  $\beta$ - and  $\gamma$ -secretase, with subsequent increase in the content of  $\beta$ -amyloid [36, 37].

Another theory is related to the reduction in the elimination of  $\beta$ -amyloid, whose cerebral clearance can be done by microglial capture or by the insulin-degrading enzyme. However, insulin competes with  $\beta$ -amyloid, which contributes to the accumulation of  $\beta$ -amyloid in the brain [38, 39]. Lowering insulin sensitivity may result in the activation of glycogen synthase kinase 3 $\beta$  (GSK3 $\beta$ ) enzyme, which catalyzes the phosphorylation of tau protein, a major component of neurofibrillary tangles [40]. Insulin and insulin-like growth factor bind to insulin receptor, leading to its autophosphorylation and activation. Activation of this receptor leads to phosphorylation of phosphoinositide-3 kinase enzyme, which in turn phosphorylates and inhibits GSK3 $\beta$  enzyme that is important for tau protein phosphorylation. Thus, insulin deficiency/resistance leads to GSK3 $\beta$  abnormal activation, and consequently, to an increase of p-tau formation [41].

Today, there is no doubt that one of the leading factors in the development of cognitive impairment in DM is *chronic hyperglycemia*, the manifestation of which is associated with cognitive deficits. The results of many studies in patients with diabetes of both types have demonstrated a close relationship between glycemia and glycated hemoglobin with 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 was found between cognitive functions and the index of postprandial glycemia [42].

Concerning other preclinical studies, hyperglycemia has been shown to increase A $\beta$  levels in the interstitial fluid, altering neuronal activity. It seems that high glucose metabolism may alter ATP-sensitive potassium channels, which correlate with changes in metabolism, neural activity, and interstitial fluid A $\beta$  [43, 44]. 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 — advanced glycation end products (AGEs), which have the property to modify neurofibrillary tangles and beta-amyloid plaques, which obviously contributes to the progression of neurodegeneration in AD.

In addition to the mechanisms discussed earlier, studies have reported that AGEs induce neuronal death through activation of cell death pathways, in addition to stimulating APP processing through increased expression of  $\beta$ - and  $\gamma$ -secretases (BACE and PSEN1), in a process involving reactive oxygen species generation [45]. Moreover, A $\beta$  peptide may undergo non-enzymatic glycation, making AGE more neurotoxic than its non-glycated form [46].

Therefore, according to the scientists, the better control of blood glucose levels is necessary to prevent the development of cognitive impairment of different origin in patients with type 2 DM [42]. At the same time, the issue of maximum advantages of compensation for type 2 DM is controversial. Thus, in a number of studies, satisfactory glycemic control was associated with less pronounced cognitive impairment [47, 48]. In contrast, the ACCORD-MIND study, conducted in 52 clinical centers 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 [49]. In addition, such an approach may be dangerous in terms of the hypoglycemic reactions risk, which adversely affects cognitive function [50, 51], because normal brain functions depend 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 focal tissue ischemia and the manifestation of vascular events [52].

In recent years, the hypothesis about the role of *hyperamyli-naemia* in the development of AD has been actively discussed [53–55]. Amylin (or islet amyloid polypeptide, IAPP) is a neuroendocrine hormone secreted by beta cells together with insulin. By interacting with the nuclei of the brain, it regulates the feeling of fullness through central mechanisms, reduces appetite, gastric emptying rate, and also suppresses glucagon secretion, preventing postprandial hyperglycemia. Today, amylin is considered the third islet pancreatic hormone (along with insulin and glucagon), which is involved in maintaining glucose homeostasis. In this case, hyperamyli-naemia, 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  $\beta$ -cells by amplifying the processes of apoptosis and/or necrosis and thereby increasing the development rate of absolute insulin deficiency. A recent study has shown that polymorphism of the amylin gene is associated with AD [53]. Independent studies have shown that elderly patients with AD or moderate cognitive impairment had lower amylin plasma concentrations than controls [54]. The brain tissue analysis of people with AD, which runs on the background of the DM, revealed the deposition of a significant amount of amylin in the gray matter and in the walls of the brain vessels. It was also demonstrated that IAPP (amylin) aggregates are able to enhance the aggregation of A $\beta$ , providing a potential additional link between AD and type 2 DM. Clearly, future studies will provide further keys to understanding the relation between cognitive decline, obesity and type 2 DM [55].

It is noteworthy that this substance was found in the brain of patients with AD without diabetes [56]. In view of the above, amylin analogs are used as an informational and non-invasive challenge test for AD [57].

*Hypertension* as a component of MS is associated with an increased risk of developing AD [58]. Noteworthy is the fact that hypertension, especially when it presents in middle age, adversely affects older age cognitive performance and this association decreases with age [59].

Hypertension adversely affects the vascular wall, which can lead to hypoperfusion, ischemia and cerebral hypoxia, and can also cause the dysfunction of the blood-brain barrier. This creates the preconditions for the accumulation of APP and A $\beta$  [60].

*Dyslipidemia* is another manifestation of MS associated with the risk of AD. Patients with AD have a 10 % higher cholesterol level compared to healthy people [61]. Hypercholesterolemia has been shown to impair the integrity of the blood-brain barrier [62].

According to experimental studies, hypercholesterolemia is associated with increased beta-amyloid deposition, cognitive deficits, neuroinflammation and cholinergic neuron dysfunction [63, 64].

Some scientists point out the beneficial effect of statins for the prevention of the progression of AD [65, 66]. However, other studies to date have not demonstrated the benefits of statins in AD [66, 67].

The results of recent studies have shown the role of gut microbiota disorders in patients with obesity in the development of neuroinflammation and, as a consequence, increased risk of AD. According to some authors, the microbiota-gut-brain axis is a bidirectional communication system that is not fully understood, but it includes neural, immune, endocrine, and metabolic pathways [69, 70]. The increased permeability of the gut and blood-brain barrier induced by microbiota dysbiosis may mediate or affect AD pathogenesis and other neurodegenerative disorders, especially those ones, which are associated with aging. In addition, bacteria populating in the gut microbiota can secrete large amounts of amyloids and lipopolysaccharides, which might contribute to the modulation of signaling pathways and the production of pro-inflammatory cytokines associated with the pathogenesis of AD. Moreover, imbalance in the gut microbiota can induce inflammation that is associated with the pathogenesis of obesity, type 2 DM, and AD. The purpose of this review is to summarize and discuss the current findings that may elucidate the role of the gut microbiota in the development of AD.

Taking into account the pathogenetic mechanisms already mentioned above, it should also be remembered that in most cases, obesity is the result of an *unhealthy lifestyle*. In addition to malnutrition, due to damage to the musculoskeletal system, patients with obesity are prone to hypodynamia, which can directly affect cognitive processes. On the other hand, cognitive impairment contributes to impaired self-care, reduced compliance, leading to the development and progression of obesity. Thus, modifying eating habits and lifestyle to prevent the development of obesity should be key point in the prevention of AD.

The relevance of this problem is confirmed by the fact that at the Society for Neuroscience recent annual meeting, several research teams presented data on mechanisms that may hamper brain energy metabolism in Alzheimer's

disease and potentially contribute to cognitive decline [71]. At the same time, clinical researchers are exploring ways to slow or prevent dementia using drugs and lifestyle modifications typically prescribed for metabolic disorders such as diabetes or obesity. These aspects have taken on new urgency as several amyloid-targeted therapies for Alzheimer's disease have failed in clinical trials, leading to questions about whether the so-called amyloid hypothesis may be flawed. Further research is needed in this direction.

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### Ожиріння і хвороба Альцгеймера

**Резюме.** В оглядовій статті наведені сучасні відомості щодо епідеміології і чинників ризику хвороби Альцгеймера при ожирінні. Проаналізовано дані літератури щодо основних патогенетичних ланок розвитку нейродегенеративних порушень у пацієнтів із ожирінням і метаболічним синдромом, а також механізмів взаємообтяження. Наведені результати клінічних

та експериментальних досліджень щодо можливостей патогенетичної корекції когнітивних порушень при хворобі Альцгеймера, яка перебігає на тлі ожиріння, зазначені найбільш перспективні напрямки наукових досліджень із цієї проблеми.

**Ключові слова:** ожиріння; метаболічний синдром; хвороба Альцгеймера; когнітивні порушення

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### Ожирение и болезнь Альцгеймера

**Резюме.** В обзорной статье приведены современные сведения об эпидемиологии и факторах риска болезни Альцгеймера при ожирении. Проанализированы данные литературы по основному патогенетическому звеньям развития нейродегенеративных нарушений у пациентов с ожирением и метаболіческим синдромом, а также механизмам взаимообтяжения. Представлены результаты клинических и эксперименталь-

ных исследований относительно возможностей патогенетической коррекции когнитивных нарушений при болезни Альцгеймера, которая протекает на фоне ожирения, указаны наиболее перспективные направления научных исследований по данной проблеме.

**Ключевые слова:** ожирение; метаболіческий синдром; болезнь Альцгеймера; когнитивные нарушения