Common pathogenetic factors in metabolic syndrome and dementia

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Abstract

Metabolic syndrome (MetS) is characterized by a defined cluster of clinical conditions which include hypertension, impaired glucose tolerance, visceral adiposity and dyslipidemia. Dementia is group of symptoms which have in common deterioration in cognitive function, more than expected from the age of individual, and Alzheimer's disease (AD) is the most common formo f dementia. Prevalence of both MetS and dementia, including AD, is growing at explosive rate worldwide, both conditions are multifactorial and there is a growing evidence of increased risk of dementia in patients with MetS. In this review, we described the potential underlying role of main components of MetS in the mechanism of pathogenetic changes in dementia. The main pathophysiological factors that contribute to dementia are non-ischemic neurodegeneration and/or neuronal death with accompanying neuroinflammation, and vascular injury. Specific components of MetS may cause or exaggerate all these changes in individual patient, leading to worsening or accelerating cognitive decline. Better understanding and recognition of the role and mechanism of MetS components as potential underlying factors in dementia, is expected to have a beneficial role in prevention and treatment of dementia, as many of MetS components may be influenced on with appropriate change of habits and therapy.

Keywords: metabolic syndrome, vascular complication, diabetic, Alzheimer disease, cognition disorders, dementia

Sažetak:

Zajednički patogenetski čimbenici u metaboličkom sindromu i demenciji
Metabolički sindrom (MetS) je obilježen definiranom skupinom kliničkih stanja koja uključuju hipertenziju, smanjenu toleranciju glukoze, visceralni oblik pretilosti i dislipidemiju. Demencija je skupina simptoma koje karakterizira progresivno pogoršanje intelektualnih sposobnosti sve do narušavanja socijalnog i radnog funkcioniranja, više nego što se očekivalo u odnosu na dob osobe. Najčešći oblik demencije je Alzheimerova bolest (AD). Prevalencija MetS-a i demencije, uključujući AD, raste eksplozivnom brzinom širom svijeta, oba stanja su multifaktorska i sve je više dokaza o povećanom riziku od demencije u bolesnika s MetS-om. U ovom preglednom radu opisana je potencijalna uloga glavnih komponenti MetS-a u patogenetskom mehanizmu demencije. Glavni patofiziološki čimbenici koji doprinose demenciji su neishemijska neurodegeneracija i/ili neuronska smrt s pratećom neuroinflamacijom, kao i promjene krvnih žila. Specifične sastavnice MetS-a mogu uzrokovati ili pogoršati sve ove promjene različito kod pojedinih bolesnika, što dovodi do pogoršanja kognitivnih funkcija odnosno ubrzanog razvoja demencije.Očekuje se da će bolje razumijevanje i prepoznavanje

uloge i mehanizma komponenti MetS-a kao potencijalnih patofizioloških čimbenika u demenciji imati korisnu ulogu u prevenciji i liječenju demencije, jer se na mnoge komponente MetS-a može utjecati odgovarajućom promjenom navika kao i adekvatnim liječenjem.

KLJUČNE RIJEČI: metabolički sindrom, vaskularna komplikacija, dijabetička, Alzheimerova bolest, kognitivni poremećaji, demencija

INTRODUCTION

In parallel with an aging population, the number of patients with dementia is continuously growing, especially in developing countries. According to recent reports, more than 55 million people currently live with dementia worldwide, and there are nearly 10 million new cases every year (1). The number of patients with dementia is expected to rise to 78 million in 2030 and 139 million in 2050 (1). As a chronic, disabling syndrome, dementia has a significant social impact and it is followed by many psychological, economic, and other consequences that influence not only on an individual patient's life, but they affect the whole family and carers.

Dementia is a disorder that is characterized by a decline in cognition affecting one or more cognitive functions: learning and memory, language, executive function, complex attention, perceptual-motor, and social cognition. (2) Among different types of dementia, Alzheimer type of dementia (or Alzheimer's disease, AD) is the most common, with 60-70% of cases (1).

AD is defined as progressive impairment of cognitive functions followed by memory loss with two characteristic pathological hallmarks: extracellular accumulation of amyloid-β peptides that form amyloid plaques, and intraneuronal finding of neurofibrillary tangles predominantly composed of aggregates formed by hyperphosphorylated Tau-protein. (3, 4, 5) These two conditions lead to increased inflammatory response in the central nervous system (CNS) followed by oxidative stress and neuronal degeneration. (6) The most important risk factor for the development of AD is the age of an individual, as more than 90-95% of cases occur in people that are older than 65 years (late-onset AD), and only 5-10% of all cases affect younger people, mostly 30-60 years old (7). The latter, early-onset AD is often inherited as familial AD with an autosomal-dominant manner, where genes coding proteins amyloid precursor protein (APP) presenilin 1 (PSEN1) and presenilin 2 (PSEN2) are affected. (7, 8, 9, 10). However, in AD patients both with early- and late-onset, the main genetic risk for the development of AD is ε4 variant of gene for apolipoprotein E (*APOE4*), especially in women (11, 12, 13). Besides age and genes as the main known risk factors, several other factors can contribute to the pathogenesis of the disease, including diet, lifestyle, alcohol, smoking, and pollutants, and AD is today considered a multifactorial disease with a complex interplay between genetic, epigenetic and environmental factors (3, 10). Women have more predisposition for AD, they are more vulnerable to brain injury caused by Tau-aggregation, and recently this predisposition was linked to higher levels of an enzyme X-linked ubiquitin-specific peptidase 11 (USP-11) both in women and experiments in female mice (14).

Vascular dementia (VD) is the second by order common type of dementia (30% of cases with dementia) This term relates to a cluster of different conditions affecting primarily the circulatory system (15). AD is often present with coexisting VD, and these two conditions may augment each other's influence on a patient's cognitive deterioration (16, 17). Other types of dementia are much less common, and they are caused by various other factors and conditions that affect the brain directly or indirectly They are classified as frontotemporal, Lewy body dementia, unspecified dementia and mixed dementia (17); they are not topic in this review.

Metabolic syndrome (MetS) is a condition characterized by a defined cluster of clinical conditions which include hypertension, impaired glucose tolerance, central (or visceral) adiposity, and dyslipidemia, and together they are known as a "deadly quartet" (18, 19, 20, 21). This infamous name relates to the fact that MetS presents a well-known group of independent risk factors that, when present together, significantly increase total cardiovascular morbidity and mortality and are also associated with the development of type 2 diabetes mellitus (T2DM) which *per se* is one of the greatest burdens of disease worldwide. At first, MetS was described by Reaven in 1988. under the name "syndrome X" (18), but the clinical definition of MetS was revised several times over years, and the final criteria were adopted in 2009. by the cooperation of several world associations (WHO- IDF, National Heart, Lung, and Blood Institute, American Heart Association, World Heart Federation, International Atherosclerosis Society, and International Association for the Study of Obesity) (21). The latest definition includes at least three out of a total of five cardio-metabolic abnormalities: elevated blood pressure >130/85 mmHg; central type (visceral) adiposity with waist circumference >102 cm in men and > 88 cm in women; insulin resistance with fasting glucose concentration > 6,1 mmol/L (2h after the meal

>7,7 mmol/L); elevated serum triglycerides level > 1,7 mmol/L; atherogenic dyslipidemia with serum low-density lipoproteins (LDL) level > 2,59 mmol/L and low serum high-density lipoprotein (HDL) level < 1, 04 mmol/L in men and < 1, 29 mmol/L in women (21). It is estimated that 25% of the world population suffers from MetS, and in people older than 40 years this percentage raises to 40%. Such a high prevalence is responsible for the fact that MetS becomes a growing public health problem with a huge socio-economic impact.

More than a fact it causes significant mortality from cardiovascular complications and T2D, clinical conditions associated with MetS, i.e. obesity, hypertension, hyperglycemia, and dyslipidemia; present also emerging risk factors for several other chronic and potentially fatal conditions like several types of cancer, non-alcoholic fatty liver disease, arthritis caused by hyperuricemia, infections and cognitive decline (22, 23, 24).

Metabolic syndrome, insulin resistance, diabetes type 2, and dementia

The connection between MetS and cognitive decline, including AD, is known for years, and it is still a topic of active investigation. A link between clinical changes associated to MetS, and loss of cognitive function has been confirmed in several studies (23, 25, 26) Mild cognitive impairment (MCI), a condition that lies between normal cognitive aging regarding age and social factors like education; and AD, more severe neurological disease was also linked to MetS, but this connection was not causatively proven (27). Insulin resistance with hyperinsulinemia, as a component of MetS and type 2 diabetes mellitus (T2DM) are a known risk factor for cognitive decline, from MCI to AD (28 6, 29; 30; 31, 32, 33, 34). Luchsinger et al. in their study reported that hyperinsulinemia doubles the risk of AD. (35).

In an extensive observational study that encompassed 89,708 diabetic patients, Gudala and al. reported a 73% increased risk of all types of dementia, a 56% increased risk of AD, and a 127% increased risk of VD. (36) Even mild, subclinical hyperglycemia, in the non-diabetics, was shown to cause significant atrophy in hippocampus and amygdala, aging-sensitive brain regions (37; 38); the other studies that performed neuromaging techniques in diabetic patients have found pathomorphological changes in many brain regions, including parietal regions, posterior cingulate cortex, and precuneus which have been linked with corresponding cognitive and other neurological symptoms (39). These data about the role of hyperglycemia in pathogenesis of dementia gave rise to a new term, type 3 diabetes (T3DM), as a neurometabolic disorder (40, 41)

Hyperinsulinemia and impaired insulin signaling share some common pathophysiological features with AD, as they are both characterized with changes in metabolism and dysfunction of the vascular system. In a recent systematic review, after filtering original articles on proteomic analysis of serum biomarkers in patients with AD and T2DM, Pereira et al. performed a meta-analysis of 22 studies on AD and 12 studies on T2DM comparing serum biomarkers in T2DM and AD. They found an overlapping of total of 17 proteins among the total present 205 proteomic biomarkers for AD and 149 for T2DM, which were differentially expressed in both diseases compared to the control. Many of these proteins were part of lipid metabolism, and some of them belonged to apolipoproteins (A1, A4, B100, and E). Some of the shared biomarkers were part of immune system molecules, like complement component C4 and constant (C) region of immunoglobulins, which is consistent with the fact of involvement of immune factors in both diseases (33). Although T2DM and AD affect different compartments – AD is primarily CNS disease and T2DM primarily affects multiple peripheral organs and cells, especially myocytes, adipocytes, and hepatocytes, they share many pathogenetic similarities. Both diseases show increased incidence in parallel with age (6, 33) and they are slowly progressive with long-term asymptomatic periods and they have complex, multifactorial pathogenesis. Furthermore, in both diseases impaired insulin signaling has an essential role in pathogenesis (42). In diabetic patients, there are several pathophysiologic mechanisms that may lead to dementia. The most common pathway for vascular dementia (but also important in other types of dementia) is mediated by increased atherosclerosis in larger cerebral arteries, leading to decreased oxygen supply. The other common vascular diabetic complication is diabetic microangiopathy, which affects small cerebral vessels and causes complications in a way of lacunar infarctions and other types of hypoxic injuries. Other noxious pathways leading to dementia include different mechanisms of neurodegeneration, which may occur because of accumulation of amylin, or increased oxidative stress that leads to mitochondrial dysfunction, and activation of enzymes that mediate aberrant neuronal and/or glial signaling (23)

In AD patients, defective insulin signaling is one of the consistent characteristics of the disease (42, 43). In normal conditions, insulin produced in pancreatic beta-cells can pass blood-brain barrier (BBB) and blood-cerebrospinal fluid barrier, via a selective active transport mechanism across endothelial cells in BBB, or receptor-mediated endocytosis via tanycytes in circumventricular organs (43). The concentration of insulin in the brain is much smaller than insulin plasma concentration, but it is proportional to peripheral insulin concentration, suggesting that the source of brain insulin comes from peripheral blood (42, 43). Insulin receptors (IR) are abundantly expressed in different parts of the brain and the expression is higher in some regions, like the olfactory bulb, hypothalamus, hippocampus, cerebral cortex, striatum, and cerebellum (44, 45, 46). In the brain, several isoforms of IR have different distributions and they show differences in affinity toward insulin or IGF-1, which is linked with distinct signaling pathways and effects on the target cell (44, 45). Insulin may be even produced *de novo* locally in the brain, but there is still no consistent proof for functional insulin secretion, and the regulatory loop of insulin secretion and utilization is not well-investigated in the brain. It is interesting that insulin

mRNA expression was found in post-mortem human brain samples, especially in the hippocampus and hypothalamus. In AD patients, this expression was decreased in comparison to control brain tissues (42, 47). A significant difference between insulin's role on the periphery and its role in the brain is that GLUT4, an insulin-sensitive transporter, is expressed only in restricted brain areas, mostly in the hippocampus and hypothalamus, so insulin has a much less significant role in the regulation of glucose uptake in most of the brain regions, which predominantly express insulin-insensitive transporters GLUT1 and GLUT5, depending of the cell type (46). Although insulin is not essential for the transport of glucose in the brain, it has an important regulatory role in glucose metabolism and many other functions that may be independent of IGF-1 or may overlap with IGF-1, like regulation of protein synthesis, cell growth, and proliferation as other cell-specific functions. The expression of insulin receptors is especially prominent in brain areas that control memory, behavior, and food intake (48). Transport of glucose, both in the brain and in the periphery, is affected by a number of factors, including obesity, inflammation, glycemia, diabetes mellitus, and levels of circulating triglycerides (46).

An important mechanism of neurodegeneration in the most common dementia, AD, includes brain insulin resistance and impaired brain glucose metabolism, with accompanying neuroinflammation and oxidative stress. Brain insulin resistance is also present in other neurodegenerative diseases like mild cognitive decline, depression, and Parkinson's disease (46), but also in MetS, obesity, and T2DM. How brain insulin resistance participates in neurodegeneration in AD, is still unknown at the molecular level. It seems that insulin signaling may be important for a decrease of the formation of amyloid plaques and normal clearance of Aβ oligomers, as whole-brain/neuron insulin receptor knockout (NIRKO) mice had increased levels of phosphorylated tau (49). Adding insulin or IGF-1 had a beneficial effect in AD model mice, decreasing cognitive deficits and increasing clearance of Aβ oligomers (46, 50) Impaired insulin signaling leads to changes in mitochondrial function, decreased ATP synthesis, and increased oxidative stress, with the release of damage-associated molecular patterns in the neuronal microenvironment. This can activate an inflammatory response, triggered by activation of transcriptional factor NF-kappa B, which is responsible for stimulation of immune cells (microglia and resident macrophages) to release inflammatory cytokines, IL-1, TNF-a, and IL-6. These cytokines, in turn, are responsible for damage to the BBB barrier, and an influx of inflammatory molecules from the blood into the brain, that may accelerate neurodegeneration. (51, 52, 53). Currently, dementia is much more recognized as one of the main complications in DM, although the mechanisms that lead to hyperglycemia-induced neurodegeneration are still under investigation. It is expected and partially proven that good glycemia control and an increase of peripheral insulin sensitivity by administration of antidiabetic agents could have a beneficial effect on cognition and dementia prevention. Some studies indicate that the administration of a new generation of antidiabetic agents that inhibit the inactivation of incretins glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) by dipeptidyl peptidase-4 (DPP-4) inhibitors, is linked with beneficial effects on mini-mental state examination (MMSE) test in subjects with dementia (54). However, a study by Tseng CH et al. in 2021. on a large sample of subjects (54) showed no association of vildagliptin therapy or incretin therapy with lower dementia risk in new-diagnosed type 2 diabetes patients followed up for dementia diagnosis. (55). Currently, there is no convincing evidence about the DPP-4 inhibitor's protective or therapeutic effect on cognition (54). One of the problems may be the less availability of systemic antidiabetic therapy in human CNS because BBB prevents the entering of most of the molecules into CNS. A much more protective effect mediated by DPP-4 inhibitor was noticed in animal models in which breaking of BBB was induced by streptozocin, so the antidiabetic agent was more available locally in CNS. (55)

Obesity, metabolic syndrome and cognitive decline in alzheimer's disease

An important component of MetS is obesity, and it is involved both in the pathogenesis of AD and in its progression. Similar to the case of hyperglycemia and diabetes, obesity has a complex role in the pathogenesis of AD, which can be direct and indirect. The relationship between risk for AD and body weight is not clear. The risk curve posing in the relationship between body mass index (BMI) and AD is actually U-shaped, i.e. the risk for AD is the highest in individuals with low BMI < 18,5 kg/m² (56) On the other side, obesity, especially visceral (abdominal) obesity in midlife acts as an independent factor that contributes to cognitive decline and development of neurodegeneration in AD. (23, 57). Obesity can act indirectly through the induction or promotion of other conditions: atherosclerosis, hypertension, and diabetes mellitus, that on their own have an influence on the pathogenesis of AD. Regarding obesity as a direct causative factor in AD, epidemiological studies still do not show consistent results, or they are sometimes contradictory (58), and the mechanism of how obesity *per se* increases the risk for AD is not clear. A recent large meta-analysis of genome-wide association studies (GWAS) on AD including 71,880 cases of AD and 383,378 controls, has shown that a genetically predicted increase in BMI in the adult life period was significantly associated with a higher risk of AD, and that low birth weight was also linked with a higher risk of AD (58). These results were at least partly explained by authors by indicating the fact that low birth weight is often associated with impaired neural development, and higher birth weight is linked to better cognitive development and "brain reserve" for later life. (58). Despite the inconsistent epidemiological data about obesity and risk for AD, numerous studies showed the existence of pathological changes in CNS in obese or

adipose patients. In adolescents with MetS, lower cognitive performance and reductions in brain structural integrity, especially the smaller hippocampal volumes, have been proven with MRI and neuropsychological evaluation (59) Although the number of participants in this study was relatively small (total 111), the study is important in the context of the increasing prevalence of childhood obesity, because MetS in young age is a predictor of the future health risk of complications of MetS and cognitive impairment in the same individuals as adults. Hippocampal reduction and cognition impairment were also detected in adults with MetS and adolescents with MetS and T2DM (59)

It is known that habits like a sedentary lifestyle with consuming a high-fat diet, in addition to genetic influence present common risk factors for AD, MetS, and T2DM *via* causing obesity-induced neuroinflammation (23) Insulin resistance, both in the brain and peripheral tissues, may be caused by obesity and it can be linked to long-term feeding with saturated fat diet, which is a common habit in MetS and T2DM patients. Feeding of AD mice with a high-fat diet has induced impaired memory, and a decrease in insulin receptor signaling in hippocampal microvessels (60, 61, with the accelerated accumulation of extracellular amyloid Aβ (62). Furthermore, even in the IRS2 KO AD mouse model, which develops insulin resistance before the development of amyloid plaques, feeding with a high-fat diet accelerated the formation of Aβ deposits. This effect was reversible, at least in the early stages, because when after high-fat diet mice were switched to caloric restriction and chow feeding, this change of diet reduced Aβ deposition in the AD mouse model (62).

The current view that tries to explain the mechanism by which obesity and lipid metabolism disbalance in MetS could lead to neurodegeneration in AD, focuses on neuroinflammation. Like in the case of systemic low-grade chronic inflammation that is observed in MetS, obesity, and T2DM, similar or identical factors (hyperinsulinemia, atherogenic adipokines, high concentration of free fatty acids and LDL-cholesterol) can contribute to changes in CNS physiology. It is well-known that adipocytes act as endocrine cells and in conditions of hypertrophy they secrete a variety of proinflammatory cytokines and adipokines. Most of all, they produce proinflammatory cytokines IL-1, IL-6, and tumor necrosis factor a (TNF-a), in an orchestra with other resident cells (mostly macrophages) in adipose tissue (51, 63). These cytokines activate vascular endothelium inducing the expression of adhesion molecules and stimulating the transmigration of immune cells in the tissues. Proinflammatory cytokines activate microglia in CNS and induce increased permeability of BBB., especially at sites of circumventricular organs (area postrema, arcuate nucleus, and subfornical organ). Activation of microglia is followed by induction of transcriptional factor NF-kappaB and further release of IL-1, IL-6 and other inflammatory cytokines (51, 52), which has the strong proinflammatory effect, so the inflammation amplifies on the systemic and local, CNS level (51, 53, 64, 53). Chronic low-grade inflammation in the hippocam-

pus, hypothalamus, and other brain areas important for memory and cognitive functions can further act by causing increased production of amyloid beta, reactive oxygen species, and other reactive mediators of cellular stress. Despite this established view of how systemic and local inflammation can cause neurodegeneration in AD, attempts to treat AD by targeting inflammation or by immunosuppression were not successful (65, 66). Interestingly, Schwartz's team made an observation that migration of blood-borne myeloid cells into CNS had a neuroprotective effect, and it led to a new, different approach in the treatment of experimental AD by boosting the immune system with reduction of regulatory T-cells or administration of checkpoint inhibitors (monoclonal antibodies targeting inhibitory immune cell receptors PD-1L or PD-1) in two mouse models of AD in an advanced stage of disease, and these therapies reduced the Aβ plaques in the brain (65). The mechanism behind this was not elucidated, but boosting of the immune system can be responsible for better stimulation of recovery in CNS areas affected by AD plaques, and it seems that here microglia can have an essential role. Microglia, as the main innate immune cells in CNS, can behave differently in various conditions, very similar to macrophages in peripheral tissues (67) In AD, the inflammatory activity of microglia is dominant over microglial-mediated clearance and neuroprotective effect, which becomes compromised.

Regarding the role of MetS and obesity in cognitive decline in AD, an imbalance of adipokines is an additional factor that can contribute to neurodegeneration. Elevated plasma levels of leptin together with leptin resistance were noticed in T2DM, MetS, and obesity

In the last several years, investigations on AD pathogenesis focused much more attention on the role of disturbed metabolism of cholesterol and other lipids in CNS. As mentioned above in the Introduction section, the main known genetic risk in patients with late-onset AD is the presence of the *APOE4* gene, which is highly involved in the control of lipid metabolism, especially cholesterol and triglycerides, because it codes carrier protein important for lipid transport. In knock-out mice for *APOE4*, amyloid plaques fail to form (13). This gene is also a well-known genetic risk factor for cardiovascular disease, and metabolic syndrome, and it is linked with decreased lifespan (13), which indicates that some common mechanisms could be involved in the pathogenesis of all three conditions, but the precise role of APOE4 is still unclear on the cellular level. A recent study by Sienski et al. has shown disrupted cellular lipid homeostasis in APOE4-expressing human induced pluripotent stem cell (iPSC)-derived astrocytes and in yeast expressing human APOE4, with intracellular lipid accumulation. Among individuals with AD, 10% higher levels of plasma cholesterol concentration were detected in comparison with healthy controls (68, 69). Therapy with statins, which decrease plasma LDL-cholesterol levels and lower cardiovascular risk, was reported to possibly lower the risk of AD and this protective effect was dependent on statin type, sex, and ethnicity (70). A pathomorphological explanation for

the involvement of cholesterol in the formation of AD amyloid deposits is still under investigation, but it was demonstrated that lipid membranes containing cholesterol promote aggregation of amyloid Aβ42 isoform, with increased cooperativity in the interaction of multiple cholesterol molecules with Aβ42 (12). Brain cholesterol turnover is different from that in the peripheral compartment because the entry of cholesterol from peripheral plasma is prevented due to BBB, so the cholesterol is mostly synthesized *de novo* in astrocytes and neurons. Normal cholesterol metabolism in the brain is important for essential neurophysiologic processes, including memory and synaptic plasticity. Normally, the enzyme hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase determines the rate-limiting step in the synthesis of cholesterol, while cytochrome P450 46A1 (CYP46A1) controls the clearance of cholesterol from the CNS and mediates its conversion into 24-hydroxycholesterol. More than 90% serum 24-hydroxycholesterol has an origin from the brain, as 24-hydroxycholesterol can easily pass BBB, and enter into the systemic circulation, from where it can be metabolized. Polymorphism of CYP46A1 was linked to AD (71) When CYP46A1 function is deficient, as in CYP46A1- knockout mice, clearance of cholesterol is impaired in CNS, so cholesterol-esters are accumulated in the brain which was connected with the formation of amyloid Abeta prom amyloid precursor protein (APP) (12, 72)

In a search for good biochemical markers for screening, early detection, and following the disease course in AD patients, members of lipid metabolism are possible candidates, although most of them, including total plasma cholesterol, LDL-cholesterol, and serum triglyceride levels, are not specific for AD. Having in mind that all of these markers are valuable also for the estimation of cardiovascular risk, metabolic syndrome, and T2D, their determination is useful for detecting the overall risk for early death in an individual. Lower levels of serum 24-hydroxicholesterol and elevated levels of CSF 24-hydroxicholesterol and other oxycholesterols may be a marker for both mild cognitive impairment and AD (73, 74). Recently, an imaging experimental method with great potential for the detection of cholesterol metabolism in the living brain was developed, as a variant of PET with the utilization of CYP46A1-targeted positron emission tomography (PET) tracer (75)

Arterial hypertension as a part of metabolic syndrome and its role in alzheimer disease

Although arterial hypertension is a direct and strong risk factor for vascular dementia, it is considered an important possible risk factor also for all other types of dementia, including AD (17). The description of the pathogenesis of arterial hypertension development in MetS exceeds the aim of this review, but it is important to pinpoint some pathophysiological consequences of hypertension on cognition and its role in dementia. It is clear that hypertension *per se* can cause damage to brain regions important for cognition (23). Pathophysiological mechanisms that lead to CNS injury are changes in small vessel autoregula-

tion and cerebral hypoperfusion, endothelial dysfunction, neuroinflammation and increased permeability of BBB, demyelination and impaired remyelination (23). The study was performed in 2016. that used combined neuroimaging analysis of more than 7700 brains and multiple biomarker analysis indicates that an important early pathological event during late-onset AD development is brain vascular dysregulation (76). In parallel with disease progression, a vicious circle is established, as deposits of amyloid around small cerebral vessels may, even more, impair clearance of amyloid beta and cause hypoperfusion, which tend to cause progression of the disease. (77) The results of different studies, including a meta-analysis study by Ding et al., suggest that taking antihypertensive therapy decreases the risk for AD (78, 79)., and beneficial effect could be achieved with combination of therapy that targets components of MetS, like combination of antihypertensives and statins, according to individual patient's indication. (48, 79)

Conclusion

Components of metabolic syndrome; i-e. hypertension, hyperglycemia, obesity, and dyslipidemia together with vascular complications are important factors in the pathogenesis of dementia. Both MetS and dementia are complex conditions with multiple factors that participate in their pathogenesis, and the number of new cases shows an explosion in the last several years with a tendency of rising even more. Diet and lifestyle could influence the risk for both metabolic syndrome and dementia, and studies suggest that a midlife history of disorders that affect the vascular system, such as hypertension, type 2 diabetes, and obesity, increase the risk for dementia including Alzheimer's disease (AD) (15, 34). It is not known whether metabolic syndrome causes dementia directly, or changes in CNS caused by mechanisms linked with dementia cause hyperglycemia associated with MetS and T2DM. Although the precise mechanism explaining the relationship between all these conditions remains unsolved, there is a fact that all components of MetS, and dementia, progressively increase with age and they act one on another which may accelerate development of complications and leads to early mortality. There is still no effective causative therapy for dementia. On the other side, there is the possibility to influence all components of MetS (hypertension, hyperglycemia, obesity, and dyslipidemia), and dementia, with adequate prevention and therapy, in a way of changing lifestyle habits (diet and better nutrition, less calory intake, and more physical activity, less smoking and alcohol), and adjusting adequate therapy according to individual's indication. Adequate prevention and screening, early diagnosis, and adjusted therapy may have beneficial effects in the prevention and retard the progression both of metabolic syndrome and dementia.

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ABBREVIATIONS:

AD – dementia of the Alzheimer type
BBB – blood-brain barrier
CNS – central nervous system
CYP46A1 - cytochrome P450 46A1
DM – diabetes mellitus
DPP-4 – dipeptidyl-dipeptidase 4
GIP – glucose- dependent insulinotropic polypeptide
GLP-1 – glucagon-like peptide 1
GLUT – glucose transporter
GWAS – genome-wide association study
HDL – high-density lipoprotein
IGF-1 – insulin-like growth factor 1
IL – interleukin
IR – insulin receptor
KO - knockout
LDL – low-density lipoprotein
MetS – metabolic syndrome
MMSE test – mini-mental state examination test
T2DM – type 2 diabetes mellitus
TNF-alpha – tumor-necrosis factor alpha
VD – vascular dementia