Poveznica mentalnoga zdravlja, pretilosti i arterijske hipertenzije

Association of mental health, obesity and arterial hypertension

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SAŽETAK: Napredak u prevenciji bolesti i zdravstvenoj zaštiti produžio je očekivano trajanje života i time povećao globalno opterećenje bolestima. Tako su nezarazne bolesti, uključujući arterijsku hipertenziju, dijabetes i demenciju, nedostatno prepoznat problem svjetske populacije. Demencija povezana sa starenjem ireverzibilno je stanje koje se očituje progresivnim padom kognitivnih funkcija te se smatra jednim od vodećih zdravstvenih problema novog doba. U zbrinjavanju ove fragilne populacije potreban je interdisciplinaran pristup jer su u osnovi patofiziološkoga zbivanja hiperinzulinemija i oksidativni stres na razini cijelog organizma, a ne izoliranog samo jednog organa.

SUMMARY: The progress in disease prevention and health care has prolonged life expectancy, thus increasing the global disease burden. The non-communicable diseases such as arterial hypertension, diabetes mellitus and dementia have been recognized as an inadequately clarified problem in the population all over the world. Senile dementia is an irreversible condition manifested by progressive decline of cognitive functions and considered as one of the leading health problems today. Proper care for this fragile population requires interdisciplinary approach because the pathophysiological events are underlain by hyperinsulinemia and oxidative stress at the whole body level rather than isolated to a single organ.

KLJUČNE RIJEČI: mentalno zdravlje, hiperinzulinemija, oksidativni stres, zdravlje srca i bubrega.

KEYWORDS: mental health, hyperinsulinemia, oxidative stress, heart and kidney health.

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Svjetska zdravstvena organizacija procjenjuje da 35,6 milijuna ljudi diljem svijeta boluje od demencije i očekuje se da će se taj broj utrostručiti do 2050. godine[1].

Alzheimerova bolest i vaskularni kognitivni poremećaji najčešći su uzroci demencije u starijoj populaciji[2]. Sve je više dokaza koji označuju da Alzheimerova bolest i vaskularni kognitivni poremećaj dijele zajedničke patofiziološke mehanizme[3]. No, s obzirom na to da su i cerebrovaskularne bolesti i Alzheimerova demencija česte u starijih osoba koje su češće i pretile, koegzistencija ovih dviju stanja može biti i slučajna[4]. Alternativno, vaskularna bolest može promicati Alzheimerovu demenciju i obratno, što rezultira međusobnom interakcijom koja pojačava njihove negativne učinke, dok kognitivni učinak ovisi o težini Alzheimerove patologije i o lokaciji vaskularnih lezija[5]. Vaskularni čimbenici rizika, koji uključuju arterijsku hipertenziju, dijabetes,

According to the World Health Organization estimates, 35.6 million people in the world suffer from dementia and this figure is expected to triple by the year 2050[1].

Alzheimer's disease and vascular cognitive disorders are the most common causes of dementia in elderly population[2]. There is increasing evidence for Alzheimer's disease and vascular cognitive disorders to share common pathophysiological mechanisms[3]. Although both cerebrovascular disease and Alzheimer's dementia are frequently present in the elderly who also suffer from obesity, the coexistence of these two conditions may also be quite accidental[4]. Alternatively, vascular disease may promote Alzheimer's dementia and *vice versa*, resulting in their interplay that enhances their negative effects, whereas cognitive effect depends on the severity of Alzheimer pathology and vascular lesion localization[5]. Vascular risk factors

hiperlipidemiju, pušenje, fibrilaciju atrija i povišenu razinu homocisteina, povećavaju rizik od demencije neovisno o pridruženom povećanju rizika od moždanog udara[6]. Nadalje, metabolički sindrom, koji sjedinjuje inzulinsku rezistenciju, arterijsku hipertenziju i dislipidemiju, povezuje se s nižim kognitivnim učinkom[7]. Moždani je udar jedan od najjačih prediktora pojavnosti demencije[8]. Pretilost visokoga stupnja podrazumijeva u najvećemu broju slučajeva hiperinzulinemiju i dijabetes[9], što se smatra rizičnim čimbenikom za nastanak demencije[10-15].

Utjecaj debljine na razvoj demencije

Povišeni indeks tjelesne težine (BMI) u srednjoj životnoj dobi povezan je s povećanim rizikom od demencije[16]. Abdominalna pretilost koja je udružena s inzulinskom rezistencijom i kardiovaskualrnim bolestima čimbenik je rizika za nastanak Alzheimerove bolesti[17]. Povišeni BMI u dobi od 70, 75 i 79 godina također je povezan s povišenim rizikom od demencije[18]. S druge strane, rezultati nekih istraživanja nisu pokazali povezanost između povišenog BMI-ja u starijoj životnoj dobi i demencije[19], dok je u drugih pronađena povezanost nižeg BMI-ja s razvojem Alzheimerove bolesti[20]. Razlog tomu može biti činjenica da je opseg struka bolji pokazatelj debljine od BMI-ja[21]. Obilježje starenja jest povećanje udjela masnoga tkiva većinom bez dobivanja na masi, pa stoga te promjene ne uzrokuju povećanje BMI-ja te su tradicionalna mjerenja debljine manje korisna u starijih osoba[21]. Utvrđeno je da u mlađih starijih osoba (65–76 godina) postoji povezanost između BMI-ja i Alzheimerove bolesti u obliku krivulje slova U, dok je u starijih starih osoba (> 76 godina) viši BMI povezan sa smanjenim rizikom od Alzheimerove bolesti, kao i da je veći opseg struka povezan s većim rizikom od Alzheimerove demencije u mlađih starijih osoba, ali ne i u starijih. Od temeljne je važnosti povezanost inzulinske rezistencije s endotelnom disfunkcijom žila, što je začetnik aterosklerotskoga procesa[22,23]. U stanju inzulinske rezistencije, koja je temeljni patofiziološki čimbenik metaboličkog sindroma i pretilosti, smanjuje se sinteza dušičnog oksida i narušuje se ravnoteža u korist vazokonstriktornih čimbenika i oksidativnoga stresa koji se smatra i osnovicom vaskularne demencije[24].

Smanjeno otpuštanje dušičnog oksida uzrokuje povećanu agregaciju trombocita i otpuštanje faktora rasta u stijenci svih krvnih žila. Osim toga, u razvoju pretilosti, kao i arterijske hipertenzije zbog protrahiranoga mineralokortikoidnoga djelovanja glukokortikoida zbog kroničnoga stresa, dolazi do daljnjega gomilanja i odlaganja masnih stanica u tijelu i pogoršanja inzulinske rezistencije, što je povezano s daljnjim remodeliranjem ciljnih organa, prije svega srca i bubrega s potrebnošću „krosdisciplinarnih" intervencija u ovoj, fragilnoj skupini bolesnika koja ima povišen rizik od morbiditeta i mortaliteta, neovisno o dobi[25,26].

Atrofija temporalnog režnja rano je obilježje demencije i kognitivnog pada i pokazatelj je neuronalne degeneracije[27,28] te je povezana s povišenim vrijednostima BMI-ja izmjerena 24 godine prije mjerenja atrofije kompjutoriziranom tomografijom (CT)[29] te sa smanjenim volumenom mozga utvrđenim magnetnom rezonancijom (MRI) u presječnome istraživanju muškaraca i žena u dobi od 44 do 60 godina[30]. Osobe s višim vrijednostima BMI-ja pokazuju veću stopu progresije atrofije mozga, što je ustanovljeno serijskim snimkama magnetne rezonancije[31]. Centralna pretilost (omjer struka i bokova) u

include arterial hypertension, diabetes mellitus, hyperlipidemia, smoking, atrial fibrillation and elevated homocysteine level, which all increase the risk of dementia independently of the associated increase in the risk of stroke[6]. Furthermore, metabolic syndrome that includes insulin resistance, arterial hypertension and dyslipidemia has been related to a lower cognitive effect[7]. Stroke is one of the strongest predictors of the onset of dementia[8]. High-grade obesity is implied in most cases of hyperinsulinemia and diabetes[9], which is considered a risk factor for development of dementia[10-15].

Impact of obesity on development of dementia

Elevated body mass index (BMI) in middle age is associated with an increased risk of dementia[16]. Abdominal obesity, which is associated with insulin resistance and cardiovascular disease, is a risk factor for Alzheimer's disease[17]. Elevated BMI at the age of 70, 75 and 79 years also is associated with a higher risk of dementia[18]. On the other hand, some studies failed to demonstrate an association between increased BMI in advanced age and dementia[19], whereas others found lower BMI to be associated with the development of Alzheimer's disease[20]. The reason for these discrepancies may be the fact that waist circumference is a better indicator of obesity than BMI[21]. Aging is characterized by an increased proportion of adipose tissue, mostly without mass gain; therefore, these changes do not lead to BMI increase and the traditional measurements of obesity are less useful in the elderly[21]. It has been found that in early old age (65-76 years), there is an U-shaped association of BMI and Alzheimer's disease, whereas in older age groups (>76 years) higher BMI is associated with a lower risk of Alzheimer's disease. Also, greater waist circumference is associated with a higher risk of Alzheimer's dementia in early old age but not in older age groups. Crucial is the association of insulin resistance and vascular endothelial dysfunction for triggering the process of atherosclerosis[22,23]. In the state of insulin resistance, which is a basic pathophysiological factor of the metabolic syndrome and obesity, the synthesis of nitric oxide is decreased and the balance impaired in favor of vasoconstrictory factors and oxidative stress, which is considered the basis of vascular dementia[24].

Reduced nitric oxide release leads to increased platelet aggregation and growth factor release in all vascular walls. Besides this, due to the protracted mineralocortical action of glucocorticoids induced by chronic stress, development of obesity and arterial hypertension is associated with further accumulation and deposition of adipose cells in the body and deterioration of insulin resistance, which is related to additional remodeling of target organs, primarily the heart and the kidney. These events require 'cross-disciplinary' interventions in this fragile group of patients at an increased risk of morbidity and mortality irrespective of age[25,26].

Temporal lobe atrophy is an early feature of dementia and cognitive decline, and an indicator of neuronal degeneration[27,28]; it was related to elevated BMI values measured 24 years before atrophy measurement by computed tomography (CT)[29] and to a reduced brain volume as determined by magnetic resonance imaging (MRI) in a cross-sectional study including men and women aged 44-60[30]. Individuals with higher BMI values showed a greater rate of brain atrophy progression as assessed by serial MRI[31]. In a cross-sectional

presječnom je istraživanju povezana s atrofijom temporalnog režnja, što je također zaključeno primjenom magnetne rezonancije[32].

Jedne od glavnih posljedica pretilosti jesu inzulinska rezistencija i hiperinzulinemija koje čine složenu interakciju autonomnoga živčanog i hormonalnog sustava te neuronskih mehanizama koji povezuju gastrontestinalni sustav s centralnim sustavom homeostaze energije[9]. Inzulin prelazi krvno-moždanu barijeru i ulazi u središnji živčani sustav iz periferije te se s amiloidom β (Aβ) „natječe" za razgradnju inzulin degradirajućim enzimom (IDE) u mozgu, uključujući i hipokampus[33]. Inzulin se proizvodi i u mozgu, gdje ima povoljan učinak na razgradnju Aβ. Periferna hiperinzulinemija može inhibirati produkciju moždanog inzulina, što dovodi do smanjenja razgradnje Aβ i povećanog rizika od Alzheimerove bolesti[34]. Studija u kojoj je istraživan utjecaj rosiglitazona na smanjenje inzulinske rezistencije i smanjenje koncentracije perifernog inzulina, utvrdila je da rosiglitazon može imati povoljne učinke i na smanjenje tegoba vezanih za Alzheimerovu demenciju[35].

Arterijska hipertenzija i Alzheimerova bolest

Alzheimerova bolest tradicionalno je smatrana neurodegenerativnim stanjem koje je uzrokovano neuronalnom disfunkcijom, koja je posljedica nakupljanja β-amiloidnih plakova i neurofibrilatornih čvorova nastalih zbog neuronalnih citoskeletnih abnormalnosti[36]. Međutim, patološki i eksperimentalni dokazi ukazuju da vaskularni čimbenici, uključujući arterijsku hipertenziju, imaju važnu ulogu u patogenezi Alzheimerove bolesti[37]. To se posebno odnosi na hipertenziju u srednjoj životnoj dobi, za koju se smatra da pridonosi riziku od razvoja Alzheimerove bolesti u kasnijoj životnoj dobi i ubrzava njezinu progresiju. Nadalje, atrofija mozga, amiloidni plakovi i neurofibrilatorni čvorovi posebice su prsutni u mozgu bolesnika s anamnestičkim podacima o arterijskoj hipertenziji u srednjoj životnoj dobi.

Hipertenzija također uzrokuje promjene krvnih žila mozga (srca i bubrega), što uzrokuje hipoperfuziju, ishemiju i hipooksiju, a to može potaknuti patološke procese Alzheimerove bolesti. Prema tome, povišeni arterijski tlak uzrokuje cerebrovaskularne promjene koje povećavaju vjerojatnost da osobe s Alzheimerovom encefalopatijom razviju sindrom demencije[38]. Rezultati nekoliko istraživanja pokazali su da hipertenzijom inducirane lezije i Alzheimerova demencija mogu imati aditivne ili sinergističke učinke te da uzrokuju ozbiljnije kognitivne poremećaje nego svaki proces pojedinačno[3]. U čak 50 % slučajeva demencija je uzrokovana miješanom patologijom koja sadržava vaskularne i neurodegenerativne lezije (amiloidne plakove i neurofibrilatorne čvorove)[39]. Arterijska hipertenzija obično prethodi nastanku Alzheimerove bolesti i kao takva može imati ulogu u njezinoj progresiji. S druge strane, smanjenje arterijskoga tlaka koje nastupa kada je Alzheimerova bolest već potpuno razvijena vjerojatno je povezano s promjenama u centralnoj autonomnoj jezgri koja kontrolira arterijski tlak, kao što je C1 područje u rostralnoj ventrolateralnoj meduli[40]. Redukcija tjelesne aktivnosti, dehidracija i malnutricija povezane su s razvijenom demencijom[38]. Iako arterijska hipertenzija promiče razvoj amiloidnih plakova rano u tijeku bolesti, patološke promjene inducirane Alzheimerovom bolešću uzrokuju redukciju arterijskoga

study, central obesity (waist to hip ratio) was associated with temporal lobe atrophy, also demonstrated by MRI[32].

One of the main sequels of obesity is insulin resistance and hyperinsulinemia, which represent a complex interplay of the autonomic nervous system and hormonal system with neuronal mechanisms connecting gastrointestinal system with the central system of energy homeostasis[9]. Insulin crosses the blood-brain barrier and enters the central nervous system from periphery, then competing with amyloid β (Aβ) for degradation by the insulin degrading enzyme in the brain, also including the hippocampus[33]. Insulin is also produced in the brain, where it exerts a favorable effect on Aβ degradation. Peripheral hyperinsulinemia may inhibit the production of brain insulin, which leads to a reduced Aβ degradation and an increased risk of Alzheimer's disease[34]. A study investigating the effect of rosiglitazone on the reduction of insulin resistance and concentration of peripheral insulin, used in the management of diabetes showed that rosiglitazone might have favorable effects also on reduction of problems related to Alzheimer's dementia[35].

Arterial hypertension and Alzheimer's disease

Alzheimer's disease has been traditionally considered a neurodegenerative condition caused by neuronal dysfunction, consequential to the accumulation of β-amyloid plaques and neurofibrillary tangles formed due to neuronal cytoskeletal abnormalities[36]. However, pathologic and experimental evidence suggests that vascular factors including arterial hypertension play a major role in the pathogenesis of Alzheimer's disease[37]. This in particular refers to middle age hypertension, which is considered to contribute to the risk of developing Alzheimer's disease later in life and to accelerate its progression. Furthermore, brain atrophy, amyloid plaques and neurofibrillary tangles are especially pronounced in the brain of patients with a history of arterial hypertension in their middle age.

Hypertension also leads to changes in vascular walls of the brain (heart and kidney), causing hypoperfusion, ischemia and hypoxia, which in turn can trigger pathologic processes of Alzheimer's disease. Accordingly, elevated arterial pressure induces cerebrovascular lesions that increase the likelihood of developing dementia syndrome in individuals with Alzheimer's encephalopathy[38]. Results of some studies have shown that the hypertension induced lesions and Alzheimer's dementia can have additive or synergistic effects, and that they in combination cause more severe cognitive disorders than any of the processes alone does[3]. In as many as 50 % of cases, dementia is caused by mixed pathology consisting of vascular and neurodegenerative lesions (amyloid plaques and neurofibrillary tangles)[39]. Arterial hypertension usually precedes the onset of Alzheimer's disease and as such may play a role in its progression. On the other hand, arterial pressure decrease that occurs when Alzheimer's disease has fully developed, probably is related to changes in the central autonomic nucleus that regulates arterial pressure, such as C1 area in the rostral ventrolateral medulla[40]. Reduced physical activity, dehydration and malnutrition are associated with developed dementia[38]. Although arterial hypertension favors development of amyloid plaques early in the course of the disease, pathologic changes induced by Alzheimer's disease lead

tlaka u kasnijim fazama, što može uzrokovati hipoksemiju i ishemiju te pridonosi pogoršanju demencije[41]. S obzirom na rastuću epidemiju pretilosti i poveznice hiperinzulinemije s dijabetesom, a dijabetesa s povišenim rizikom od Alzheimerovu bolest otvara se mogućnost i novih strategija u prevenciji i liječenju navedenih stanja[42].

Zaključak

Jedna od glavnih posljedica pretilosti jesu inzulinska rezistencija i hiperinzulinemija, koje označuju složenu interakciju autonomnoga živčanog i hormonalnog sustava te neuronskih mehanizama koji povezuju gastrointestinalni, srčanožilni i bubrežni sustav sa centralnim sustavom homeostaze energije. Na narušavanje sustava energijske homeostaze zbog prekomjernog unošenja hrane i/ili fizičke neaktivnosti moguće je utjecati multifaktorskim intervencijama kako bi se „poremećena" ravnoteža ispravila.

to arterial pressure reduction in later stages, which can cause hypoxemia and ischemia, thus contributing to exacerbation of dementia[41]. Considering the growing epidemic of obesity and the association between hyperinsulinemia and diabetes, and between diabetes and an increased risk of Alzheimer's disease, there is room for novel strategies in the prevention and treatment of these conditions[42].

Conclusion

Insulin resistance and hyperinsulinemia as the main sequels of obesity represent complex interaction of autonomic nervous system and hormonal system with neuronal mechanisms connecting gastrointestinal, cardiovascular and kidney system with the central system of energy homeostasis. Impairment in the system of energy homeostasis due to excessive food intake and/or physical inactivity can be influenced by multifactorial interventions to correct the imbalance.

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