UNIVERSITY OF MEDICINE AND PHARMACY OF CRAIOVA

DOCTORAL SCHOOL

STUDY OF INFLAMMATORY AND METABOLIC PROCESSES IN A GROUP OF PATIENTS WITH COGNITIVE IMPAIRMENT

PH. D. THESIS - ABSTRACT

PH.D SUPERVISOR,
PROF. UNIV. DR. SIMONA GUSTI

STUDENT – PH.D. CANDIDATE
DR. CĂTĂLINA COTEANU

CRAIOVA
2018

CONTENTS

Key words: mild cognitive impairment, metabolic syndrome, chronic inflammation, ratio triglycerides-HDL cholesterol, ratio diastolic velocity-resistance index.

INTRODUCTION

The metabolic syndrome, a constellation of parameters taken individually, increases the risk of cardiovascular disease, having as central elements insulin resistance and visceral obesity.

Recent research has raised new elements of great importance such as low-grade chronic inflammation, which together with the elements of the metabolic syndrome, affecting structures of the central nervous system produces changes in higher brain function such as memory, attention, language or executive function.

This paper, through an ample clinical and paraclinical study, attempts to evaluate a possible association between metabolic syndrome and biological inflammatory syndrome in cognitive status change and the stratification of the risk of cognitive decline depending on certain components of the metabolic syndrome and the presence of chronic inflammation, using the classical method, as well as modern methods, such as ultrasonographic vascular exploration.

GENERAL PART - STATE OF KNOWLEDGE

1. Characteristics of clinical course of cognitive impairment

Higher brain functions (memory, attention, language, executive function) are defined as complex cerebral processes that occur in the brain, enabling the human individual to establish connections between the knowledge acquired during life. They have as a central element the memory that allows the individual to retain and evoke past experiences. [POO MM, ET AL., 2016]

These cognitive processes take place in specific cortical areas, called secondary or tertiary association areas. At their level there is a complex integration of these functions that allow the daily activities to be carried out in optimal parameters. [AMUNTS K, ZILLES K, 2015]

Mild cognitive impairment (MCI) has been defined as an intermediate condition between physiological aging and dementia. [WINBLAD B, ET AL, 2004]

There have been described two subtypes of MCI: amnestic-MCI (characterized by memory disorders) and nonamnestic-MCI (characterized by disorders in other cognitive domains). [PUSSWALD G, ET AL, 2013]

Neuropsychological examination is an essential part of the process of assessing a patient with cognitive deficits, Montreal Cognitive Assessment Scale (MoCA) being the test with the highest sensitivity and specificity in MCI. [NASREDDINE ZS, ET AL, 2005]

Evolution of MCI patients to dementia is estimated at 10 to 15% per year, amnestic MCI generally evolves towards Alzheimer's disease, while non-amnestic MCI evolves to fronto-temporal dementia or dementia with Lewy bodies. [PETERSEN RC, NEGASH S, 2008]

2. Metabolic syndrome - definitions and physiopathology considerations

In October 2009, it was published a joint statement of prestigious professional organizations, who identified the specific criteria for the clinical diagnosis of metabolic syndrome (MS). An important step that this consensus has made was that abdominal obesity should not be a mandatory condition for MS diagnosis, being just one of the five criteria. [ALBERTI K.G., ET AL, 2009]

The prevalence is increasing, especially in developing countries, and there is a global impact on almost a third of the general population. [NEMATY M, ET AL, 2014]

The first step in the onset of MS is to increase insulin resistance, particularly in people with predominant central obesity. The metabolic syndrome involves the development of several complex processes that are in a close interconnection, thus proving both the genetic component and the strong involvement of environmental factors. [STANCAKOVÁ A, LAAKSO M, 2014]

Another aspect that has generated increased interest was the understanding of the link between metabolic abnormalities and subsequent physiopathological effects, and in this sense the connection between obesity and chronic inflammation has emerged as a conclusion of proinflammatory cytokines that are overexpressed in obesity. There are also studies that show a correlation between vascular brain changes and this "dysmetabolic" syndrome. [GUZIK TJ, ET AL, 2017]

Ratio triglycerides – HDL cholesterol has been proposed on a large scale as an atherogenic marker, a ratio over 3 has the best specificity and sensitivity for diagnosing increased insulin resistance in overweight patients. [RUSSO I, 2012]

There have also been described associations of metabolic syndrome with subtypes of cognitive impairment and in relation to the presence of chronic inflammation. [ROBERTS RO, ET AL, 2010]

3. Physiopathology features of the inflammatory syndrome

Inflammation is a complex defense reaction that occurs in a vascularized tissue, which appear in response to tissue injury. Through this reaction the body tends to remove the etiological agent that caused the aggression and promote healing. Under certain circumstances, when the answer is inappropriate, it can become harmful and can become chronic. [GAZIANO TA, ET AL, 2007]

Chronic inflammation can be triggered by cellular stress. The greatest danger is that acting silently has a very high destructive capacity, it can persist undetected for decades, leading to cell death. [LAWRENCE T, GILROY DW, 2007]

Inflammation has two components that occur locally: vascular changes and cellular changes, these being triggered by inflammatory mediators that are released locally and is spreading systemically, thus generating an acute phase system response. [LIBBY P, HANSSON GK, 2015]

Recent research identifies mitochondrial dysfunction that occurs with age as the main actor of chronic inflammation. At the level of deteriorated and dysfunctional mitochondria

an inflammatory mediator may occur known as the "inflammasome", which is a regulator of the innate immune response. [GREEN DR, ET AL, 2011]

Of the markers of chronic inflammation IL-6 and C-reactive protein were the most studied. C-reactive protein (CRP), synthesized in the liver, is one of the acute-phase reactants the most sensitive to tissue destruction and inflammation. Increased high responsive C-reactive protein (hCRP) is strongly associated with the increased risk of cardiovascular disease, as well as stroke. [KAPTOGE S, ET AL, 2010]

Inflammatory markers may be raised before the onset of cognitive decline, which shows that their determination for certain people can be used for an early diagnosis of cognitive impairment. [SINGH T, NEWMAN AB, 2011]

SPECIAL PART –PERSONAL CONTRIBUTIONS

4. Material and Methods

The ***aim of the study*** was the observation of a possible association relationship between metabolic syndrome and biological inflammatory syndrome in modifying cognitive status and stratification of the risk of cognitive decline depending on certain components of the metabolic syndrome and the presence of chronic inflammation.

Research objectives:

- Quantification of clinical and paraclinical parameters and cerebral vascular parameters in a group of patients with cognitive deficits.
- Establishing predictive factors in the emergence and accentuation of cognitive disorders.
- Establishing correlations between cognitive degradation, the presence of chronic inflammation and metabolic status, to achieve a stratification scale for the risk of cognitive decline.

A prospective clinical and paraclinical clinical study was conducted over 3 years on a total of 110 patients with cognitive impairment. The patients in the study group were grouped as follows: group A, consisting of 60 patients (54.5%) who met the criteria for metabolic syndrome and group B, consisting of 50 patients (45.5%), who met at most two of the criteria for defining metabolic syndrome. The results were compared with those of a control group of 50 healthy people who were both clinically and biologically evaluated, and demographic characteristics (age and sex groups) were similar to those of the group of patients.

In both groups there is a similar gender distribution, with a ratio women: men is 1: 1.2. Patients in group A (MetS) were aged between 65 and 82 years with a mean age of 74.4 years (± 4.5), and those of group B (non-MetS) were aged between 65 and 82 years of age, with an average age of 73.8 years old (± 4.8).

The cognitive assessment of patients in the two groups was made using test MoCA and the maximum score of 30 points test MoCA was divided between four cognitive domains as: memory 9 points, attention 8 points, language 6 points, the executives 7 points. Cognitive impairment has been separated into two major categories: amnestic-MCI and nonamnestic-MCI. Each of the two categories was then subdivided according to the impact of a single cognitive domain, respectively, affecting several cognitive domains, resulting in four different entities.

For the inclusion of patients in the two groups we used the diagnosis criteria for metabolic syndrome defined by consensus in 2009. According to this definition, it is necessary to have at least three criteria out of a total of five. Note that to increase the sensitivity of the results, we also used a compound parameter found in the literature, namely the ratio triglycerides - HDL cholesterol.

Assessment of the chronic inflammatory response syndrome was made by analyzing two important markers, high sensitive C-reactive protein and fibrinogen.

The paraclinical vascular was followed and evaluation of Doppler parameters: intima-media thickness, resistance index and estimate a parameter original relationship between diastolic velocity and resistance index.

5. Results

5.1. Results on the evaluation of cognitive deficit

The overall assessment of cognitive deficit has shown quite close values between group A (MetS) and group B (nonMetS), with statistically significant differences compared to the control group.

These differences between results were maintained for each of the four cognitive domains studied.

In both groups of patients the most affected cognitive domain was memory and the least affected was language. In group A (MetS), after the memory disorder, attention and then executive function were affected, so that patients in group B (nonMetS) suffered damage to the executive function and attention after memory impairment.

5.2. Results on the evaluation of metabolic syndrome

Regarding the determination of the parameters of the metabolic syndrome we found that for the abdominal circumference the highest values were in the patients of group A (MetS), where average values were 85.87 cm for women and 98.71 cm for men, and for patients in group B (nonMetS) the mean values were 75.78 cm for women and 84.88 cm for men.

For triglycerides, we found average values in group A (MetS) of 184.5 mg / dl and in patients in group B (nonMetS) a mean value of 165.5 mg / dl.

Instead, the lowest HDL cholesterol mean values were in the group B patients (nonMetS) the average value was 47.78 mg / dl in women and 39.81 mg / dl in men, while in group A (MetS) the mean values were 49.39 mg / dl in women and 40.59 mg / dl in men.

Another parameter of the metabolic syndrome is blood pressure. The mean values of systolic BP were in group A (MetS) 162.8 mmHg, while in group B (nonMets) of 136.8 mm Hg; for diastolic BP, the mean values were 91.2 mmHg in group A (MetS) and 82.9 mmHg in patients in group B (nonMetS).

Blood glucose levels were also higher in the patients of group A (MetS) that we have obtained a mean value of 128.25 mg / dl, and for the patients in group B (nonMetS) these values were 95.68 mg.

All results from patients in the two groups were significantly different from the control group.

Analyzing the ratio of triglycerides to HDL cholesterol, we found that the mean value in lot A (MetS) was 4.24, while in lot B (nonMetS) the mean value was 3.96, results that also differed statistically significantly from the control group.

Regarding the distribution of patients in group A (MetS), according to the number of criteria met, we observed that the number of patients who complied with the five criteria was equal to the number who met the four criteria, which is double the number of patients who achieved only three criteria. Regarding the frequency of the criteria, we noticed that the most frequently encountered were increased blood pressure, then increased triglycerides and increased blood glucose, instead the size of the abdominal circumference and the decrease in HDL cholesterol appear in fewer cases.

We then analyzed for patients in group A (MetS) the types of associations of parameters that define the metabolic syndrome and we noticed that certain combinations such as: triglycerides + HDL cholesterol + blood pressure + glycemia occur with a nearly double frequency in women vs. males and the combination of abdominal circumference + triglycerides + blood pressure + glycemia occurs in relatively equal proportions. Note that some combinations such as abdominal circumference + triglycerides + HDL cholesterol + glycemia only appear in the group of women, while the combination of abdominal circumference + triglycerides + HDL cholesterol + high blood pressure occurs only in males.

For patients in group B (nonMetS), we noticed that in men there were several types of associations that were not encountered in the group of women (blood pressure and blood glucose, abdominal circumference and triglycerides, and abdominal circumference and blood pressure).

5.3. Results on the evaluation of inflammatory syndrome

An important parameter of inflammatory syndrome is highly sensitive C-reactive protein. hCRP average value obtained from patients in group A (MetS) was 3.05 mg / dl and for patients in group B (nonMetS) this value was 2.67 mg / dl.

Depending on the the high-sensitive C-reactive protein in group A (MetS), more than half of the patients had high sensitive C-reactive values ranging from 2 to 3 mg / dl, and a third had the values of this parameter above 3 mg / dl; in contrast, in the group B patients (nonMetS), most patients had hCRP values ranging from 2 to 3 mg / dl and only one fifth had values above 3 mg / dl.

The second parameter of the inflammatory syndrome followed in our study was fibrinogen. The mean values of fibrinogen were 338.2 mg / dl in patients in Group A (MetS), and in patients in B (nonMetS) the mean values were 300.6 mg / dl.

Regarding the distribution of patients in group A (MetS) based on fibrinogenemia values, we found that 50% of the patients had values between 250 mg / dl and 350 mg / dl, in order for more than 40% of the patients to have higher values greater than 350 mg / dl. Analyzing the distribution of patients in group B (nonMetS) based on the value of fibrinogen, we noticed that 60% of patients had values ranging from 250 mg / dl to 350 mg / dl and 20% of patients had values greater than 350 mg/dl.

All results from patients in the two groups were significantly different from the control group.

5.4. Results on the evaluation of vascular parameters

The results obtained in determining the three vascular parameters studied differed statistically significantly from those in the control group, both for patients in group A (MetS) and for patients in group B (nonMetS). Thus, the mean values recorded for the intima-media thickness (IMT) in the right and left common carotid arteries, respectively, in the right and left internal carotid arteries, were over 1 mm in the group A patients (MetS) and more than 0.9 mm in patients in group B (nonMetS), the cutt-off value being 0.9 mm.

For the calculated resistance index in the common carotid arteries and internal carotid arteries, we also obtained mean values exceeding the normal limit for both patients in group A (MetS), where the mean value of this index was above 1.01 and for patients in group B (nonMetS) where this value was above 0.85, in this case the cut-off value being 0.75.

A last parameter studied, an original parameter introduced in the literature by Professor MD Simona Gusti, was the ratio diastolic velocity-resistance index. [GUSTI S, ET AL, 2004]

In this case, the mean values obtained in patients in group A (MetS) were below the threshold of 30 and for patients in group B (nonMetS) these mean values were around 30. We recall the fact that for this parameter the mean mean values placed more than 38.

5.5. Correlations between the parameters studied in the group A (MetS)

In the Group A patients (MetS), there were significant correlations between the outcome of the MoCA test and the number of criteria met to define the metabolic syndrome (r = -0.34), as well as between the MoCA result and the triglycerides (r = -0 , 25), MoCA and HDL-cholesterol (r = 0.2), MoCA and diastolic blood pressure (r = -0.54). It should be noted that negative correlations were also found between the MoCA results and the TG / HDL cholesterol ratio (r = -0.42).

Regarding the correlation between the test result MoCA syndrome and inflammatory components, these values have been obtained with high-sensitive C-reactive protein (r = 0.3).

Also, between the MoCA test results and the vascular parameters we obtained some correlations, the best being with IMT at bilateral ACC and ACI levels, as well as the VD/IR ratio (r = -0.4).

By correlating the results obtained between each of the cognitive domains studied and the metabolic syndrome components, we noticed that there was a negative correlation between memory and triglycerides (r = -0.25), respectively between this cognitive domain and the diastolic blood pressure (r = -0.35).

5.6. Correlations between the parameters studied in the group B (nonMetS)

In the group B patients (nonMetS), there were obtained correlations between the total test result MoCA and triglycerides (r = 0.2), MoCA and HDL-cholesterol (r = 0.2), MoCA and diastolic blood pressure (r = -0.44). There were also negative correlations between the MoCA results and the TG / HDL cholesterol ratio (r = -0.36). We observed that correlations with highly sensitive reactive C protein (r = -0.32) were obtained between the MoCA test results and the components of the inflammatory syndrome. We have observed that among the components MoCA test results, there were also obtained correlations with high sensitive C-reactive protein (r = -0.32).

Also, between the results of the MoCA test and the vascular parameters, we obtained some correlations, the best being with IMT in the bilateral ACC and ACI, as well as with the VD/IR ratio (r = -0.4).

6. Discussion

The overall assessment of cognitive deficit has shown quite close values between group A (MetS) and group B (nonMetS), with statistically significant differences compared to the control group. These differences of results were maintained for each of the four cognitive domains studied.

In the group of patients with metabolic syndrome, we observed that there were associations with strong statistical significance between cognitive impairment and increased abdominal circumference, decreased HDL cholesterol, increased diastolic blood pressure, and increased triglycerides HDL cholesterol ratio. In contrast, when we analyzed the association of these parameters with non-amnestic MCI subtypes, we did not obtain any results with statistical significance except for the increase in diastolic blood pressure values, which makes this parameter more important in defining the non-amnestic MCI cognitive impairment, data found in literature. [ROBERTS RO, ET AL, 2010]

The triglycerides - HDL cholesterol ratio was significantly correlated with the intima media thickness in patients in group A (MetS) with cognitive impairment type amnestic, without getting the same statistical significance when we studied the association of the two parameters in patients in group B (nonMetS). [COTEANU C, ET AL, 2017]

In contrast, in the group B patients (nonMetS) this parameter was significantly correlated with the diastolic velocity - resistance ratio index only in patients with cognitive impairment type nonamnestic MCI, suggesting a close relationship of this parameter with cognitive impairment that does not primarily affect memory, but at least one of the other higher brain functions. [COTEANU C, COTEANU MF, 2011]

For patients in group A (MetS), we obtained correlations with statistical significance at the association of diastolic blood pressure with the intima media thickness, results that did not reach statistical significance in patients in group B (nonMetS), suggesting a link between the increase in diastolic blood pressure (even isolated) and cognitive decline of any type in patients with defined metabolic syndrome. [COTEANU C, ET AL, 2015]

Speaking of the association between diastolic blood pressure and highly sensitive reactive C protein, it is noted that in this case there were statistically significant correlations for the patients in both groups, this suggesting a link to this parameter with chronic inflammatory changes occurring in patients who do not necessarily have a defined metabolic syndrome. [COTEANU C, ET AL, 2013]

For patients in group B (nonMetS), we observed the association of amnestic MCI subtypes only with increased triglycerides and increased triglycerides - HDL cholesterol ratio. In contrast, for patients with nonamnestic MCI, we did not achieve any statistically significant results, except for the increase in diastolic blood pressure values, which again highlights the value of this parameter in defining the non-amnestic MCI cognitive impairment.

In the group B patients (nonMetS) for non-amnestic MCI subtypes, we obtained association with statistical significance only of the ratio diastolic velocity resistance index, which connects this parameter more of that subtype cognitive impairment .

Regarding the correlations between metabolic syndrome parameters with vascular parameters in patients in group B (nonMetS), we found that the associations with statistical significance were only for the correlation of triglycerides - HDL cholesterol ratio with the ratio diastolic velocity resistance index, in patients with cognitive impairment of type nonamnestic MCI.

Recall that these correlations were met and patients in group A (MetS) with severe type nonamnestic MCI, which comes to reinforce the special contribution that the original parameter can bring disorder to diagnose cognitive type nonamnestic, irrespective of whether or not patients have inflammatory syndrome, there are data on the association of this parameter with other pathologies. [COTEANU A, ET AL, 2013]

Another highly statistically significant correlation obtained from patients in group B (nonMetS) was the ratio of HDL cholesterol triglyceride with high sensitive C-reactive protein.

Another high statistical correlation obtained in group B patients (nonMetS) was that of the triglycerides- HDL cholesterol ratio with high sensitive C-reactive protein. Note that this correlation was only obtained for patients in group B (nonMetS) for non-amnestic MCI subtypes, suggesting a link between changes in lipid (incipient) metabolism with chronic inflammatory syndrome in patients who did not primarily affect memory, but the damage occurred in other cognitive domains.

7. Conclusions

1. We conducted a comprehensive and complex research of a group of patients with cognitive impairment, with and without metabolic syndrome, research in which we used non-invasive methods of exploration: MoCA test, evaluation of metabolic syndrome parameters and inflammatory syndrome, cerebral vascular examination by Doppler ultrasound, this being less mentioned in the literature.

2. We used an original Doppler vascular parameter, ratio diastolic velocity-resistance index in this study, to evaluate the degree of resistance in cerebral circulation, these together with the triglycerides - HDL cholesterol ratio, have not been used for the evaluation of patients with MCI.

3. The triglycerides-HDL cholesterol ratio was significantly correlated with the intima media thickness in patients in group A (MetS) with amnestic cognitive impairment type.

4. The triglycerides-HDL cholesterol ratio was significantly correlated with the diastolic velocity-resistance ratio index in group B patients (nonMetS) with nonamnestic cognitive impairment type.

5. For patients in group A (MetS) we obtained correlations with statistical significance when associating diastolic blood pressure with the intima media thickness, this fact suggesting a link between elevated diastolic blood pressure (even isolated) and cognitive decline of any type in patients with defined metabolic syndrome.

6. For patients in group B (nonMetS) we obtained a statistically significant association between the ratio diastolic velocity-resistance index to high sensitive C-reactive protein in patients with amnestic cognitive impairment type, which may indicate a relation between changes in brain vascular resistance and chronic inflammation, setting a different pattern from the damage that involves metabolic changes associated with increased levels of high-sensitive C-reactive protein.

7. The correlation of neuropsychological tests with parameters of metabolic syndrome, parameters of chronic inflammatory syndrome and Doppler parameters, has led us to achieve some outstanding results and conclusions, relating to the establishment of specific patterns, preventing their progress towards more severe disorders that have serious socio-medical implications.

8. Selective References

1. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, Fruchart JC, James WP, Loria CM, Smith SC Jr. Harmonizing the metabolic syndrome ‑ a Joint Interim Statement of the International Diabetes Federation Task Force on Epidemiology and Prevention, National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation. 2009; 120: 1640-1645.

2. Amunts K, Zilles K. Architectonic mapping of the human brain beyond brodmann. Neuron. 2015; 88: 1086–1107.

3. Coteanu A, Gusti S, Coteanu C. The value of Doppler cerebral parameters to assess a group of patients with multiple sclerosis. Curr Health Sci J. 2013; 39(1): 31-34.

4. Coteanu C, Gusti S, Coteanu A. Association of inflammatory markers and intima - Media thickness in Mild Cognitive Impairment. Archives of the Balkan Medical Union. 2013; 48(2): 192-195.

5. Coteanu C, Gusti A, Coteanu MF, Gusti S. Relationship between individual components of metabolic syndrome and carotid intima-media thickness in mild cognitive impairment. Physiology. 2015; Supp , 36-37.

6. Coteanu C, Gusti A, Coteanu MF, Gusti S. Association of Some Components of the Metabolic Syndrome with the Subtype of Mild Cognitive Impairment. Curr Health Sci J. 2017; 43(4): 351-354.

7. Gaziano TA, Galea G, Reddy KS. Scaling up interventions for chronic disease prevention: the evidence. Lancet. 2007; 370: 1939–1946.

8. Green DR, Galluzzi L, Kroemer G. Mitochondria and the autophagy-inflammation-cell death axis in organismal aging. Science (New York, N.y). 2011; 333 (6046): 1109-1112.

9. Gusti S, Coteanu M, Gusti A. Study of the cerebral vascular Doppler velocimetry and EEG in a group of 18 cases of Alzheimer's disease. Rom J Physiol. 2004; 41 (1-2): 91-97.

10. Guzik TJ, Skiba DS, Touyz RM, Harrison DG. The role of infiltrating immune cells in dysfunctional adipose tissue. Cardiovascular Research. 2017; 113(9): 1009-1023.

11. Kaptoge S, Di Angelantonio E, Lowe G, Pepys MB, Thompson SG, Collins R, Danesh J. Emerging Risk Factors Collaboration, C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. Lancet. 2010; 375 (9709): 132–140.

12. Lawrence T, Gilroy DW. Chronic inflammation: a failure of resolution?. International Journal of Experimental Pathology. 2007; 88: 85–94.

13. Libby P. History of discovery: inflammation in atherosclerosis. Arterioscler Thromb Vasc Biol. 2012; 32: 2045–2051.

14. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, Cummings JL, Chertkow H. "The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment". *J Am Geriatr Soc*. 2005; 53 (4): 695–699.

15. Nematy M, Ahmadpour F, Rassouli ZB, Ardabili HM, Azimi-Nezhad M. A Review on Underlying Differences in the Prevalence of Metabolic Syndrome in the Middle East, Europe and North America. J Mol Genet Med. 2014; S1: 019.

16. Petersen RC, Negash S. Mild cognitive impairment: An overview. CNS Spectr. 2008; 13: 45–53.

17. Poo MM, Pignatelli M, Ryan TJ, Tonegawa S, Bonhoeffer T, Martin KC, Rudenko A, Tsai LH, Tsien RW, Fishell G, Mullins C, Gonçalves JT, Shtrahman M, Johnston ST, Gage FH, Dan Y, Long J, Buzsáki G, Stevens C. The present state of the engram. BMC Biol. 2016; 14: 40.

18. Pusswald G, Moser D, Gleiß A, Janzek-Hawlat S, Auff E, Dal-Bianco P, Lehrner J. Prevalence of mild cognitive impairment subtypes in patients attending a memory outpatient clinic—Comparison of two modes of mild cognitive impairment classification. Results of the Vienna Conversion to Dementia Study. Alzheimer's Dement. 2013; 9: 366–376.

19. Roberts RO, Geda Y E, Knopman DS, Cha R H, Boeve BF, Ivnik R J, Pankratz VS,Tangalos EG, Petersen R C. Metabolic Syndrome, Inflammation, and Non-Amnestic Mild **Cognitive Impairment in Older Persons: A Population-Based Study. Alzheimer disease and associated disorders. 2010; 24 (1): 11-18.

20. Russo I. The Prothrombotic Tendency in Metabolic Syndrome: Focus on the Potential Mechanisms Involved in Impaired Haemostasis and Fibrinolytic Balance. Scientifica. 2012;;2012: 525374.

21. Singh T, Newman AB. Inflammatory markers in population studies of aging. Ageing Res Rev. 2011; 10 (3): 319–329.

22. Stančáková A, Laakso M. Genetics of metabolic syndrome. Rev Endocr Metab Disord. 2014 Dec; 15(4): 243-252.

23. Winblad B, Palmer K, Kivipelto M, Jelic V, Fratiglioni L, Wahlund L, Nordberg A, Bäckman L, Albert M, Almkvist O. Mild cognitive impairment–beyond controversies, towards a consensus: Report of the International Working Group on Mild Cognitive Impairment. J. Intern. Med. 2004; 256: 240–246.