COGNITIVE IMPROVEMENTS FOLLOWING BODY MASS REDUCTION INDUCED BY INTRAGASTRIC BALLOON PLACEMENT IN MORBIDLY OBESE PATIENTS. A PRELIMINARY STUDY

Michał JANEWICZ1, Marek BINDER2, Agata GAŻDZIŃSKA3, Olaf E. TRUSZCZYŃSKI4, Aleksandra MOJKOWSKA5, Piotr ZIELIŃSKI6, Stefan P. GAŻDZIŃSKI7

1 SWPS University of Social Sciences and Humanities, Warsaw, Poland
2 Institute of Psychology, Jagiellonian University, Krakow, Poland
3 Department of Pathophysiology and Flight Safety, Military Institute of Aviation Medicine, Warsaw, Poland
4 Institute of Psychology, Cardinal Stefan Wyszyński University, Warsaw, Poland
5 Department of Surgery, Military Institute of Aviation Medicine, Warsaw, Poland
6 Department of Aviation Psychology, Military Institute of Aviation Medicine, Warsaw, Poland
7 Creative Neuroscience Lab – CNS Lab, Military Institute of Aviation Medicine, Warsaw, Poland

Stefan P. Gaździński, Military Institute of Aviation Medicine, Krasińskiego 54/56 Street, 01-755 Warsaw, Poland, e-mail: stefan.gazdzinski@yahoo.com

Introduction: Obesity and type 2 diabetes mellitus (T2DM) are associated with poorer cognitive performance. Reports suggest that bariatric surgery may lead to improvements in cognitive processes. However, the potential effects of mood improvements have not yet been evaluated. The aim of the study was to assess the effects of intragastric balloon (IGB) induced weight loss on cognitive performance in morbidly obese patients and relate them to changes in mood.

Methods: Twenty four morbidly obese patients (43.9±12.0 years of age, 145.6±22.3kg, body mass index (BMI): 49.8±6.9, 11 females, 14 with T2DM), underwent tests of visual short-term memory (Benton Visual Retention Test), sustained and divided attention (Color Trail Test), and verbal short-term memory: (Digit Span from WAIS-R) 1) a month before IGB insertion, 2) three months after, 3) one month after IGB removal. Depressive symptoms were evaluated with the Beck Depression Inventory (BDI).

Results: Significant cognitive improvement was observed over the first three months of IGB treatment in verbal short-term memory, visual short-term memory, and sustained and divided attention among all patients, regardless of their T2DM status. However, these changes correlated with weight loss only in patients without comorbid T2DM. The cognitive changes were not associated with changes in depressive symptoms. The improved cognitive performance was sustained over the last three months of the treatment.

Source of support: This study was supported by the Polish National Science Centre: grant 2013/09/B/NZ7/03763.

Author's address: Stefan P. Gaździński, Military Institute of Aviation Medicine, Krasińskiego 54/56 Street, 01-755 Warsaw, Poland, e-mail: stefan.gazdzinski@yahoo.com
INTRODUCTION

A growing body of research demonstrates that obesity is associated with poorer cognitive processes in healthy adults [14], faster cognitive decline in the elderly [36], poorer executive functions at any age [4,11,12,28,30,31]. Compared to non-obese individuals, obese individuals demonstrate lowered performance in attention switching skills, inhibition, flexibility and attention [8,35]. Finally, it was demonstrated that a larger increase in BMI in adulthood was associated with lower executive function [31]. A series of studies focused on the speed of cognitive aging among overweight and obese in twin populations demonstrated that being overweight or obese in midlife and late midlife was associated with lower cognitive skills in later life [5,15]. Moreover, it appears that people suffering from obesity are often more prone to experience distress, depression and eating disorders, such as Binge Eating Disorder, among others [17,33].

A review article by Brandao et al. [3] revealed that 20%–56% of preoperative bariatric patients have a current psychiatric diagnosis. Moreover, the authors pointed out that major depressive disorder is the most frequent condition, followed by social phobia, anxiety disorders, somatization, hypochondria, and obsessive-compulsive disorder [3]. Higher BMI [21,34] and increased visceral fat [25] are frequently reported to be associated with depressive symptoms, e.g., in adults with current depression, or a history of diagnosed depression or anxiety [34]. Obese people are not only at a higher risk of depression but depression is also a predictor of weight gain and future obesity [2,23]. Consistently, an epidemiological study of almost 44,800 (United States) nationally representative respondents [16] demonstrated that obese women and overweight (but not obese) men were more prone to depressive mood than their non-overweight counterparts; the depressive mood was operationalized by whether or not the participant reported feeling sad, blue, or depressed for more than seven days during the month prior to answering the questionnaire.

T2DM not only exacerbates these cognitive deficits, but also detrimentally affects the following cognitive domains: abstract reasoning, memory with subdomains of working memory, immediate memory and learning rate, and incidental memory, information processing speed, attention and executive function, and visuospatial skills [37]. Furthermore, morbid conditions co-occurring with obesity, such as T2DM, may be related to declines in episodic memory [27], working, and verbal memory, as well as mental flexibility [19].

Bariatric surgery is the only effective method leading to sustained long-term weight loss and reversal of medical dysfunction associated with obesity. One explanation shows that obesity and depression can be related through inflammation [26,32]. Previous neuroimaging studies suggested that bariatric surgery leads to changes in patterns of brain activity elicited by appetitive stimuli [29], improvements in memory function over just three months following the surgery [13], and improvements in attention, executive function, and memory [1]. However, performance on tests of language functioning remained stable[1]. We have demonstrated that three-month-long treatment with an intragastric balloon (IGB) leads to remission of neuroinflammation in patients with T2DM participating in this study [10].

IGB placement is an endoscopic method of obesity treatment. It is a minimally invasive procedure inducing weight loss by reducing the gastric reservoir capacity, leading to premature satiation and prolonged satiety, and modulation of hormone levels regulating energy balance. The balloon is a smooth, spherical, saline or air-filled, silicone elastomer of the size between 500 and 800 ml. There is one type of balloon adjustable in size. Balloon treatment is temporary and the balloon should be removed after six months, except for adjustable balloon, which can remain in the stomach for 12 months. This method is used for patients who 1) need a surgery, but whose excessive weight would put them risk or reduces their likelihood of good outcome, 2) patients who refuse bariatric surgery or would benefit from a “bridge” to bariat-
ric surgery (weight loss preceding the actual surgery), and 3) patients with a BMI of up to 35 with or without comorbidities, who have not achieved sustained weight loss with other methods.

Here, we evaluated if IGB treatment lasting for six month leads to improvements in short-term memory, processing speed, visual search and visual memory, and whether these changes are related to changes in depressive symptomatology and weight changes.

**METHODS**

This study was part of a larger project involving neuroimaging using magnetic resonance methods to evaluate neural changes accompanying weight loss [10]. Fourteen morbidly obese patients with co-morbid T2DM (hence labeled OD patients, 47.9±7.8 years of age, five females, 144±28kg, BMI=47.2±6.6, %EW=89±27% — excess body weight) and 10 morbidly obese patients without T2DM (hence labeled OB patients, 48.6±14.9 years of age, six females, 148±13kg, BMI=53.4±5.9, percent excess body weight, EW=114±24%) underwent pen and paper versions of tests of visual short-term memory (Benton Visual Retention Test, 37), visual search and sustained and divided attention (Color Trail Test, CTT-1, CTT-2, Polish normalization, [6], auditory attention and verbal working memory (Digit Span from WAIS-R, Polish version revised and renormalized in 2004), and depressive symptoms (Polish translation of Beck Depression Inventory, BDI, [22]: a) one month before IGB insertion, b) three months after, c) one month after IGB removal (fig. 1). They were consecutive patients qualified for saline-filled IGB treatment lasting six months between April 2015 and December 2016, who did not have contraindications for magnetic resonance. Parallel versions of these tests were utilized in random order. Depressive symptoms were evaluated at all time-points. The standard cut-off scores are as follows: 0-9 — indicates no depression; 10–18 — indicates mild depression; 19-29 — indicates moderate depression; 30-63 — indicates severe depression. All tests were performed by an experienced (MJ) in a quiet room, same every time. All procedures were performed according to manuals, in the morning hours, one on one with the psychologist; no third party observers were present. Among OD, scores of four patients indicated mild depression and scores of four patients indicated moderate depression, whereas among OB two patients were qualified as having mild depression and one as having moderate depression. No patient obtained scores qualifying as having severe depression. None of the patients reported a diagnosis of major depressive disorder, nor was taking anti-depressive medications at the time of the study.

All enrolled patients were consecutive patients qualified for IGB treatment over two years, who did not have contraindications for magnetic resonance.

Among OD patients, 11 reported hypertension, ten were taking hypertension medications. However, when their blood pressure was measured, they all met the criteria for hypertension. Seven patients had dyslipidemia (five taking medications), 10 had a fatty liver diagnosis, four were cigarette smokers; smoking is a factor known to detrimentally affect cognitive function [7]. Nine of them had a history of gastritis, seven were H. Pylori positive, two patients had cholecystolithiasis, two were after cholecystectomy because of cholecystolithiasis, two had diabetic polyneuropathy, one had diabetic retinopathy, three had obstructive sleep apnea (OSA). Twelve OD were taking metformin and three of them were taking other oral anti-diabetic medications. Three OD were taking insulin. Due to IGB treatment, two of them ceased taking insulin, another two reduced the number of types of anti-diabetic medication. Five OD had normal blood pressure after IGB removal. One patient had gastric ulcer hemorrhage caused by taking aspirin against medical prescription. It led to premature IGB removal one month prior to the scheduled time [24]. However, his scores on

---

**Fig. 1.** Timeline of the study. Patients undergo the 1st cognitive testing four weeks before IGB insertion, 2nd testing three months after, and the last, 3rd testing four weeks after IGB removal.
the tests were within the range of results obtained by other patients taking part in the study; his exclusion did not affect the results.

Among OB patients, two reported hypertension and were taking hypertension medications. Two patients had dyslipidemia (all of them were taking medications), one had a fatty liver diagnosis, and one was a cigarette smoker. Four of them had a history of gastritis, two were H. Pylori positive, one patient had cholecystolithiasis, two were after cholecystectomy because of cholecystolithiasis, and one had hypothyroidism. All the patients were Caucasian.

All participants gave written informed consent to all procedures approved by the Bioethical Commission at the Military Institute of Aviation Medicine, Warsaw, Poland (permission number 03/2013, in agreement with the Declaration of Helsinki. Written informed consent was obtained from all participants in this study.

Statistical analyses

The changes in body weight and BMI were evaluated using 2 (groups: OD vs. OB) x 3 (time-points) repeated measures ANOVA. The group effect (T2DM diagnosis) is referred to as the T2DM effect, whereas the time effect is referred to as the effect of treatment for excessive body weight.

Given the non-linearity changes in cognitive and BDI scores (tab. 1), they were evaluated using 2 (groups: OD vs. OB) x 2 (time-points) ANOVA repeated measures, separately for the first three months of the treatment (fig. 1), and for the following three months. In the analyses, time-point was used as the intra-group factor, whereas the T2DM status was used as the between-group factor. The interactions between the time-point and the T2DM status were the basis for evaluation of differences in cognitive recovery between both groups. Correlations between changes in cognitive and BDI scores were calculated using Pearson’s product-moment correlation. A significance level of p<0.05 was considered statistically significant. Given the preliminary nature of the study, no corrections for multiple comparisons were performed. All statistical tests were conducted with R version 3.4.4 (with the “ez” package developed for that version of R).

RESULTS

Weight changes induced by IGB between insertion and three months thereafter

The 2 (group) x 3 (time-point) repeated measures analyses yielded significant main effects of treatment for body weight [F(2,44)=57.45, p<0.001], and BMI [F(2,44)=60.90, p<0.001]. The main group effect was significant only for BMI [F(1,22)=6.43, p=0.02]. None of the interactions reached statistical significance. These effects in OD correspond to 10.6% and 5.1% decrease in BMI over the first three months of therapy and the following three months of therapy, whereas the corresponding BMI decreases in OB are 8.6% and 5.1%. In terms of body weight, it decreased by 10.6% and 5.4% respectively in OD, and 8.3% and 4.6%, respectively in OB.

Cognitive changes between IGB insertion and three months thereafter

The 2 (group) x 2 (time-point) repeated measures analyses yielded significant main effects of treatment for digit span [F(1,22)=4.66, p=0.042], completion time for CTT-1 [F(1,22)=4.41, p=0.048], completion time for CTT-2 [F(1,22)=4.68, p=0.042], and number of errors regarding colors in CTT-2 [F(1,22)=8.08, p=0.009]. These effects corresponded to a 9% increase in repeated digits in

| Tab. 1. Mean scores obtained at respective time points. CTT-1 time and CTT-2 time – the time needed to finish the respective tests. CTT-2 #colors - properly selected digit but wrong color. OD: BMI, OD: Body mass – mean BMI and mean body mass in patients with type 2 diabetes mellitus; OB: BMI, OB: Body mass – mean BMI and mean body mass in patients without T2DM. |
|---|---|---|
| **TP1** | **TP2** | **TP3** |
| Digit span | 12.4 ± 4.1 | 13.6 ± 4.7 | 14.2 ± 4.5 |
| CTT-1 time | 43.5 ± 10.5 | 38.8 ± 10.5 | 40.5 ± 12.3 |
| CTT-2 time | 87.3 ± 22.6 | 80.8 ± 22.6 | 78.4 ± 20.3 |
| CTT-2 #colors | 0.4 ± 0.5 | 0.0 ± 0.2 | 0.2 ± 0.4 |
| BENTON Errors | 4.2 ± 2.2 | 3.0 ± 2.8 | 3.5 ± 2.7 |
| BDI | 10.3 ± 6.8 | 10.2 ± 9.0 | 6.0 ± 6.3 |
| OD: BMI [kg/m2] | 47.2 ± 6.6 | 42.2 ± 7.3 | 39.8 ± 7.6 |
| OD: Body mass [kg] | 144.0 ± 27.6 | 128.7 ± 25.7 | 120.9 ± 25.6 |
| OB: BMI [kg/m2] | 53.4 ± 5.9 | 48.8 ± 4.6 | 46.1 ± 4.4 |
| OB: Body mass [kg] | 147.9 ± 12.8 | 135.6 ± 12.7 | 128.2 ± 14.8 |
the Digit Span test, an 8% decrease in CTT-2, as well as a 89% decrease in the number of errors regarding colors, as well as a 40% decrease in the total number of errors in the Benton test (tab. 1). Furthermore, there was an impact of treatment on the total number of errors in the Benton test [F(1,22)= 6.30, p=0.020]. Neither the main effect of T2DM status nor the interaction between the T2DM status and the treatment were significant for any measure. No significant main effects or interactions were found for the BDI scores. The mean results for each measure at each time point are provided in table 1.

Cognitive changes between three months after insertion and one month after IGB removal

No change in cognitive measures was significant between three months after IGB insertion and one month after its removal. Neither T2DB nor the interaction between T2DM status and time was significant for any measure. Similarly, for the BDI scores, none of the effects was significant.

Correlates of cognitive changes

In OD, none of the absolute changes in cognitive measures between one month before insertion and three months thereafter correlated with changes in BDI, body mass, and BMI.

However, in OB, larger weight loss and larger BMI loss correlated with a larger reduction in number of errors regarding color on CTT-2 (r < -0.641, p < 0.046), as well as larger weight loss and larger BMI loss had a correlation to improvement in digit span (r < -0.604, p=0.06).

DISCUSSION

We have observed improvements in short-term memory, visual search and memory and sustained and divided attention in morbidly obese patients during intragastric balloon treatment over the first three months of the treatment, regardless of depressive state changes (measured using the Beck Depression Inventory) and type 2 diabetes mellitus diagnosis. Interestingly, cognitive improvements correlated with decreases in body weight and BMI only in the group of patients without T2DM. However, no statistically significant changes were observed over the following three months of treatment.

These findings in general support the existing body of evidence that bariatric surgery leads to improvement in cognitive functioning [1,13]. Surprisingly, we did not find any interaction effect between T2DM diagnosis and cognitive improvement due to treatment. This is unexpected given that our magnetic resonance spectroscopy study in the same population demonstrated normalization of brain myo-inositol, a marker of neuroinflammation, only in the OD group during the treatment [10]. Similarly, T2DM was associated with more brain atrophy in the OD than in OB [9] and IGB treatment lead to some morphological brain recovery in the OD cohort (to be described separately). However, the cognitive improvements correlated with decreases in body weight and BMI only in the group of patients without T2DM; it suggests that the mechanisms of cognitive improvement in patients with and without comorbid T2DM might be different. Cognitive improvements after IGB insertion were not related to changes in depressive symptomatology. Similar findings, i.e. a lack of relationship between history of major depressive disorder preceding bariatric surgery with post-surgery cognitive improvements, were reported [1].

The lack of statistically significant changes over the last three months of treatment may be due to smaller weight loss over this period than over the first three months of treatment (tab. 1). It may also be interpreted that the observed cognitive improvements are transient, possibly associated with the effects of IGB on the host [20]. Therefore, the changes in cognition due to IGB treatment should be also evaluated long-term after IGB removal.

The major limitations of this study are the small sample size and the small/limited battery used in the assessment. Future studies should utilize comprehensive cognitive batteries and larger cohorts.

To sum up, similarly to more invasive bariatric techniques, morbid obesity treatment with the intragastric balloon leads to cognitive improvements that are related to weight loss in patients without comorbid type 2 diabetes mellitus. These improvements do not seem to be related or accompanied by significant mood changes.

ACKNOWLEDGEMENTS

We thank doctors Grzegorz Redlizs-Redlicki and Maciej Pietruszka of the Department of Surgery at Military Institute of Aviation Medicine, Warsaw, Poland for their role and selecting and referring patients. We express our gratitude to Ms. Ewelina Kaniewska and Ms. Marta Turczyńska for the collection of clinical data required for our study. We extend our gratitude to all patients and volunteers taking part in our study. Without your help the whole adventure would not be possible.
REFERENCES

1. Alosco ML, Spitznagel MB, Strain G, Devlin M, Cohen R, Crosby RD, et al. Pre-operative history of depression and cognitive changes in bariatric surgery patients. Psychology Health & Medicine. 2015; 20(7):802-13.

2. Booth HP, Prevost AT, Guliford MC. Impact of body mass index on prevalence of multimorbidity in primary care: cohort study. Family Practice. 2014; 31(1):38-43.

3. Brandao I, Fernandes AL, Osorio E, Calhau MDC, Coelho R. A psychiatric perspective view of bariatric surgery patients. Archives of Clinical Psychiatry. 2015; 42(5):122-8.

4. Cserjesi R, Molnar D, Luminet O, Lenard L. Is there any relationship between obesity and mental flexibility in children? Appetite. 2007; 49(3):675-8.

5. Dahl AK, Hassing LB, Fransson EI, Gatz M, Reynolds CA, Pedersen NL. Body mass index across midlife and cognitive change in late life. International Journal of Obesity. 2013; 37(2):296-302.

6. Dugbartey AT, Townes BD, Mahurin RK. Equivalence of the Color Trails Test and Trail Making Test in nonnative English-speakers. Archives of Clinical Neuropsychology. 2000; 15(5):425-31.

7. Durazzo TC, Gaździński S, Meyerhoff DJ. The neurobiological and neurocognitive consequences of chronic cigarette smoking in alcohol use disorders. Alcohol and Alcoholism. 2007; 42(3):174-85.

8. Fergenbaum JH, Bruce S, Lou W, Hanley AJG, Greenwood C, Young TK. Obesity and Lowered Cognitive Performance in a Canadian First Nations Population. Obesity. 2009; 17(10):1957-63.

9. Gaździński SP, Gaździńska A, Gaździńska A, Gorycka M, Pacho RA, Walecki J, et al. Type 2 Diabetes Exacerbates Structural Brain Changes in Middle-Aged Morbidly Obese Patients. ESMRMB Congress; October 2017; Barcelona, ES: Springer; 2017. p. S438.

10. Gaździński SP, Gaździńska AP, Orzeł J, Redlisz-Redlicki G, Pietruszka M, Mojkowska A, et al. Intragastric balloon therapy leads to normalization of brain magnetic resonance spectroscopic markers of diabetes in morbidly obese patients. Nmr in Biomedicine. 2018; 31(9).

11. Gunstad J, Lhotsky A, Wendell CR, Ferrucci L, Zonderman AB. Longitudinal Examination of Obesity and Cognitive Function: Results from the Baltimore Longitudinal Study of Aging. Neuropediatrics. 2010; 34(4):222-9.

12. Gunstad J, Paul RH, Cohen RA, Tate DF, Spitznagel MB, Gordon E. Elevated body mass index is associated with executive dysfunction in otherwise healthy adults. Comprehensive Psychiatry. 2007; 48(1):57-61.

13. Gunstad JSG, Devlin MJ, Wing R, Cohen RA, Paul RH, Crosby RD, Mitchell JE. Improved memory function 12 weeks after bariatric surgery. Surgery for Obesity and Related Diseases. 2011; 7(4):465-72.

14. Hassenstab JJ, Sweat V, Bruehl H, Convit A. Metabolic Syndrome Is Associated with Learning and Recall Impairment in Middle Age. Dementia and Geriatric Cognitive Disorders. 2010; 29(4):356-62.

15. Hassing LB, Dahl AK, Pedersen NL, Johansson B. Overweight in Midlife Is Related to Lower Cognitive Function 30 Years Later: A Prospective Study with Longitudinal Assessments. Dementia and Geriatric Cognitive Disorders. 2010; 29(6):543-52.

16. Heo M, Pietrobelli A, Fontaine KR, Sirey JA, Faith MS. Depressive mood and obesity in US adults: comparison and moderation by sex, age, and race. International Journal of Obesity. 2006; 30(3):513-9.

17. Hill AJ. Obesity and eating disorders. Obesity Reviews. 2007; 8:151-5.

18. Jaworowska A. Test Pamięci Wzrokowej Bentona - Polska normalizacja: Pracownia testów psychologicznych polskiego towarzystwa psychologicznego. 2013.

19. Kiunke W, Brandl C, Georgiadou E, Gruner-Labitzke K, Horbach T, Kohler H, et al. Performance in neurocognitive tasks in obese patients. Does somatic comorbidity matter? Frontiers in psychiatry. 2013; 4:84.

20. Konopko-Zubrzycka M, Baniukiewicz A, Wróblewski E, Kowalska I, Zarzycki W, Górska M, et al. The Effect of Intragastric Balloon on Plasma Ghrelin, Leptin, and Adiponectin Levels in Patients with Morbid Obesity. Journal of Clinical Endocrinology & Metabolism. 2009; 94(4):1644-9.

21. Konttinen H, Silventoinen K, Lahteenkorva SS, Mannisto S, Haukkala A. Emotional eating and physical activity self-efficacy as pathways in the association between depressive symptoms and adiposity indicators. American Journal of Clinical Nutrition. 2010; 92(5):1031-9.
22. Koziara K. Assessment of depressiveness in population. Psychometric evaluation of the Polish version of the CESD-R. Psychiatry Polska. 2016; 50(6):1109-17.

23. Luppinio FS, de Wit LM, Bouvy PF, Stijnen T, Cuijpers P, Penninx B, et al. Overweight, Obesity, and Depression A Systematic Review and Meta-analysis of Longitudinal Studies. Archives of General Psychiatry. 2010; 67(3):220-9.

24. Mojkowska A, Gaździński S, Frączek M, Wyleżol M. Gastric Ulcer Hemorrhage - a Potential Life-Threatening Complication of Intragastric Balloon Treatment of Obesity. Obesity Facts. 2017; 10(2):153-9.

25. Murabito JM, Massaro JM, Clifford B, Hoffmann U, Fox CS. Depressive Symptoms Are Associated with Visceral Adiposity in a Community-Based Sample of Middle-Aged Women and Men. Obesity. 2013; 21(8):1713-9.

26. Nemiary D, Shim R, Mattox G, Holden K. The Relationship Between Obesity and Depression Among Adolescents. Psychiatric Annals. 2012; 42(8):305-8.

27. Nilsson LG, Nilsson E. Overweight and cognition. Scandinavian Journal of Psychology. 2009; 50(6):660-7.

28. Noble JM, Manly JJ, Schupf N, Tang MX, Mayeux R, Luchsinger JA. Association of C-Reactive Protein With Cognitive Impairment. Archives of Neurology. 2010; 67(1):87-92.

29. Ochner CN KY, Conceição E, Pantazatos SP, Puma LM, Carnell S, Teixeira J, Hirsch J, Geliebter A. Selective reduction in neural responses to high calorie foods following gastric bypass surgery. Annals of Surgery. 2011; 253(3):502-7.

30. Pignatti R, Bertella L, Albani G, Mauro A, Molinari E, Semenza C. Decision-making in obesity: a study using the Gambling Task. Eating and Weight Disorders. 2006; 11(3):126-32.

31. Sabia S, Kivimaki M, Shipley MJ, Marmot MG, Singh-Manoux A. Body mass index over the adult life course and cognition in late midlife: the Whitehall II Cohort Study. American Journal of Clinical Nutrition. 2009; 89(2):601-7.

32. Simo R, Ciudin A, Simo-Servat O, Hernandez C. Cognitive impairment and dementia: a new emerging complication of type 2 diabetes-The diabetologist’s perspective. Acta Diabetologica. 2017; 54(5):417-24.

33. Simon GE, Von Korff M, Saunders K, Miglioretti DL, Crane PK, van Belle G, et al. Association between obesity and psychiatric disorders in the US adult population. Archives of General Psychiatry. 2006; 63(7):824-30.

34. Strine TW, Mokdad AH, Dube SR, Balluz LS, Gonzalez O, Berry JT, et al. The association of depression and anxiety with obesity and unhealthy behaviors among community-dwelling US adults. General Hospital Psychiatry. 2008; 30(2):127-37.

35. Wilkości M, Jaracz M, Tomaszewska M, Bielinski M, Dróżdż W, Junik R, et al. Working memory, executive function and depressive symptoms in subjects with pathological obesity. Bipolar Disorders. 2008; 10:89-90.

36. Yaffe K. Metabolic syndrome and cognitive decline. Current Alzheimer Research. 2007; 4(2):123-6.

37. Zilliox LA, Chadrasekaran K, Kwan JY, Russell JW. Diabetes and Cognitive Impairment. Current Diabetes Reports. 2016; 16(9).