

# The Biochemical Effect of Laparoscopic Sleeve Gastrectomy on Serum Magnesium Levels

DANIEL TIMOFTE<sup>1</sup>, LACRAMIOARA OCHIUZ<sup>2\*</sup>, MANUELA URSARU<sup>1</sup>, BOGDAN CIUNTU<sup>3</sup>, IOANA HRISTOV<sup>4</sup>, ION COSMIN PUJA<sup>5,6</sup>, VALENTIN CALU<sup>7</sup>, VERONICA MOCANU<sup>4</sup>

<sup>1</sup> Grigore T. Popa University of Medicine and Pharmacy, Department of General Surgery, 16 Universitatii Str., 700115, Iasi, Romania

<sup>2</sup> Grigore T. Popa University of Medicine and Pharmacy, Department of Pharmaceutical and Biotechnological Drug Industry, 16 Universitatii Str., 700115, Iasi, Romania

<sup>3</sup> Grigore T. Popa University of Medicine and Pharmacy, Department of Radiology, 16 Universitatii Str., 700115, Iasi, Romania

<sup>4</sup> Grigore T. Popa University of Medicine and Pharmacy, Department of Pathophysiology, 16 Universitatii Str., 700115, Iasi, Romania

<sup>5</sup> Iuliu Hateganu University of Medicine and Pharmacy, 8, Victor Babes Str., 400000 Cluj Napoca, Romania

<sup>6</sup> Octavian Fodor Regional Institute of Gastroenterology and Hepatology of Cluj Napoca, 19 Croitorilor Str., 400000, Cluj Napoca, Romania

<sup>7</sup> Carol Davila University of Medicine and Pharmacy, Department of General Surgery, Elias Emergency University Hospital, 37 Dionisie Lupu Str., 030167 Bucharest, Romania

*Lately it is generally accepted that bariatric surgery is one of the most effective treatment of morbid obesity. Also, the importance of studying the effects of serum magnesium levels on general health comes from data that shows that a low serum magnesium concentration increases the risk of all-cause mortality when added to the conventional cardiovascular disease risk factors. Thus, in the present report we decided to study how laparoscopic sleeve gastrectomy affects the levels of serum magnesium in obese populations. Our results showed that patients that underwent laparoscopic sleeve gastrectomy surgery had an increased circulating magnesium level. However, further detailed investigations are needed to identify the exact underlying mechanisms. Furthermore, the role of magnesium in obesity and comorbid conditions should be established, to answer the question whether or not dietary magnesium deficiency is a significant nutritional concern.*

*Keywords: magnesium, serum, body mass index, laparoscopic, obesity*

Obesity is currently considered to be one of the most common chronic diseases in Western countries [1, 2]. The growing incidence of obesity is widely recognized as one of the most challenging contemporary problems regarding the public health [3]. Obesity has been proven to lead to numerous macrovascular and microvascular complications, including myocardial infarction, diabetic cardiomyopathy, stroke, neuropathy and renal failure in many patients and is currently difficult to control by the available medical treatment, including diet, drug therapy and behavioural or biochemical modifications [4-11].

Therefore bariatric surgery should not be disregarded as a possible solution. It has been demonstrated that bariatric surgery can be one of the most effective treatment of morbid obesity and, depending on the type of operation, is also been shown that it can be very effective in the resolution of diabetes [12]. Studies demonstrated that this effect occurs even before the start of the weight loss, and it may be explained by changes in the gut hormones and the diet of the patient [13].

Regarding the specificity of Romania's population, the prevalence of obesity in the adult population in our country has previously been found to range between 7.9 % [14] and 21.7 % [15]. It is important to be mentioned that these obesity rates are self-reported through estimates of anthropometric data. Other two epidemiological studies we found, performed back in 2005 and 2006, presented an estimated obesity prevalence of 24 % and, respectively, 26.3 % [16, 17].

The importance of studying the effects of serum

magnesium levels on general health comes from data that shows that a low serum magnesium concentration increases the risk of all-cause mortality when added to the conventional cardiovascular disease risk factors [18]. In addition, the same analysis shows that low serum magnesium has a significant correlation with all-cause mortality in type 2 diabetes patients [18]. However some studies presented results that a weight-reducing surgical method, the jejunioileal bypass, has been shown to correlate with an increased risk of magnesium depletion [19]. Regarding laparoscopic sleeve gastrectomy in morbidly obese patients, there is relatively little information about possible changes in circulating magnesium concentrations [20].

Although there is no available literature studying a possible hypomagnesaemia in Romanian population, magnesium deficiency commonly occurs throughout the world. For example, in the United States, the estimated average requirement for magnesium is set at 255–265 mg/day for females and 330–350 mg/day for males. Yet, the same presented data indicates that about 60% of all adults do not meet the previous presented requirements [21]. In addition, the same data estimates that about 10% of adults older than 19 years have magnesium intakes that are about half of the US recommended dietary allowance [22, 23]. Despite this, widespread pathological conditions attributed to dietary magnesium deficiency are rarely reported.

On the other hand, epidemiological and correlation studies clearly show that a low magnesium status is associated with various pathological conditions, such as atherosclerosis [24, 25], hypertension [24,26], osteoporosis

\* email: ochiuzd@yahoo.com

[27], diabetes mellitus [28], neurological or psychiatric manifestations [28-32] and some form of cancers [33, 34]. From this data one may conclude that magnesium deficiency may be a greater nutritional problem than currently recognized. Recent findings seem to provide some possible reasons for these conflicting conclusions about the real importance of magnesium.

One of these findings is based on the connection between serum magnesium levels and inflammation in humans. Human studies clearly indicate that a low magnesium status is associated with increased inflammatory and oxidative stress. More so, C-reactive protein is a well-documented indicator of chronic inflammation [35]. In addition, several studies showed that magnesium intake was inversely related to elevated serum or plasma C-reactive protein. However, perhaps the most eloquent proof was an analysis of no less than 5,007 children (with ages ranging between 6–17 years old). This analysis found that the children who consumed less than 75% of the recommended daily allowance were 1.94 times more likely to have elevated serum C-reactive protein when compared to children who were consuming more than the recommended daily allowance for magnesium [36]. A similar analysis on an adult sample this time, showed a 1.48–1.75 times increased likelihood of elevated serum C-reactive protein for those consuming less than the recommended daily allowance for magnesium when compared with those who consumed more than the recommended dose [37].

The second recent finding is about a potential magnesium deficiency in obese populations. Recent studies show that an obese person who has a low magnesium level is much likely to present chronic inflammation indicators when compared to an obese with normal levels of magnesium. For example, in a study on 192 subjects [38], the results showed a correlation between low serum magnesium and elevated TNF- $\alpha$  concentrations in obese these subjects. In another interesting study about magnesium levels and obesity, Corica et al. [39] found that hypertensive obese subjects had significantly lower plasma magnesium concentrations than the non-obese healthy controls. But more interesting, the same study found that the obese subjects with normal blood pressure presented normal values of serum magnesium. This finding is consistent with the idea from the literature that magnesium supplementation lowers blood pressure in hypertensive, but not in normotensive, overweight populations [40].

There is still a lot to learn about the connection between chronic low-grade inflammation and obesity. Not all obese people present increased indicators of inflammatory stress. That is the reason, why many authors suggest that other factors may be involved in the development of inflammation in this population. As it was before presented, a low magnesium status occurs more often in obese populations individuals [38, 39, 41, 42], thus it is plausible to assume that one of the variable causing the activation of inflammatory responses may be a magnesium deficiency. Given this hypothesis, it is the important to study

how laparoscopic sleeve gastrectomy affects the levels of serum magnesium in obese populations.

## Experimental part

### Patients

Eighty patients (38 males and 42 females), all Romanians, hospitalized for bariatric surgery in the Surgery Service, Sf. Spiridon Clinical Emergency Hospital in Iasi (Romania) were recruited to be part of the experimental group. These patients were investigated before and after 6 months and again after 1 year following the laparoscopic sleeve gastrectomy. Data from the experimental group was compared to that of a control group, recruited from the waiting list for laparoscopic sleeve gastrectomy, consisting of 80 patients, 29 males and 51 females. The control group was recruited to match weight, body mass index (BMI) and serum magnesium in relation to the corresponding baseline values in the group who underwent laparoscopic sleeve gastrectomy. All the included patients signed an informed consent [43] and the experimental procedures were carried out in accordance with the mandatory principles of the ethics [44-49].

Baseline characteristics of the subjects are shown in table 1.

### Laparoscopic sleeve gastrectomy

Laparoscopic sleeve gastrectomy involved a longitudinal resection of the stomach on the greater curvature from the antrum starting opposite of the nerve of Latarjet up to the angle of His. The first step of the procedure was the division of the vascular supply of the greater curvature of the stomach, which was achieved with the section of the gastro-colic and gastro-splenic ligaments close to the stomach. The greater curvature was completely freed up to the left crus of the diaphragm to completely resect the gastric fundus that harbours the ghrelin secreting cells of the stomach. The second step of the procedure was the longitudinal gastrectomy that "sleeved" the stomach to reduce it to a narrow tube. A naso-gastric tube was used to obtain a precise calibration and to avoid stenosis of the gastric plasty.

All patients treated by surgical intervention were given the same kind of dietary advice and were recommended to take a daily oral supplement containing vitamins and minerals but not magnesium.

### Body Mass Index

BMI (kg/m<sup>2</sup>) was calculated as weight (kg) divided by height (m) squared.

### Magnesium levels

The serum magnesium was measured by spectrophotometric determination in serum with xylidyl blue (Architect, Abbott) [50, 51]. The coefficient of variation is <2% for this method.

### Statistics

All analyses were defined a priori. The results were given

	Experimental data	Control group	Group comparisons (p value)
Sex (male/female)	38/42	29/51	
Age (years)	40.14 (7.2)	42.03 (7.8)	0.116
Weight (kg)	122.3 (19.2)	120.8 (21)	0.629
Height (cm)	171.1 (9.7)	169.6 (7.2)	0.280
BMI (kg/m <sup>2</sup> )	43.2 (6.1)	42.4 (4.6)	0.331
Magnesium (mmol/L)	0.778 (0.11)	0.780 (0.118)	0.885

**Table 1**  
CLINICAL CHARACTERISTICS AT BASELINE IN PATIENTS BEFORE LAPAROSCOPIC SLEEVE GASTRECTOMY SURGERY AND IN PATIENTS FROM CONTROL GROUP. DATA GIVEN ARE ARITHMETIC MEAN VALUES ( $\pm$ SD). BMI=BODY MASS

as arithmetic mean with SD. ANOVA was used for group comparisons. Adjusted analyses were made using ANCOVA. Baseline associations between continuous variables were analyzed using Pearson correlation coefficients. Tests were two-tailed and a  $p$  value  $< 0.05$  was considered significant [52]. The statistical analysis was performed using Windows 19.0 version of SPSS software (SPSS Inc., Chicago, IL, USA).

## Results and discussions

### Baseline data

At baseline, before patients underwent laparoscopic sleeve gastrectomy surgery, there were no statistically significant differences between the group of patients directed for surgical treatment and the control group, regarding age, height, weight, BMI or serum magnesium concentrations (table 1). In addition, the correlations between serum magnesium concentrations on the one hand, and BMI were not statistically significant ( $r = 0.060$ ,  $p = 0.447$ ). None of the patients in this study had any complications during the surgical performance or during the 1-year follow-up period.

### Data at 6-months follow-up

Serum magnesium concentration increased in the experimental group, from 0.77 to 0.82 mmol/L ( $p = 0.005$ ), while an opposite trend was observed during the corresponding period in the control group, from 0.78 to 0.76 mmol/L ( $p = 0.238$ ). The intergroup difference in serum magnesium concentrations at the 6-months follow-up ( $p < 0.001$ ) was significant (fig. 2).

In the experimental group, the mean BMI decreased from 43.2 kg/m<sup>2</sup> at baseline to 33.2 kg/m<sup>2</sup>, ( $p < 0.001$ ). In the control group, a small change but non-significant in mean BMI was observed between baseline and 6 months follow-up, BMI 42.4 kg/m<sup>2</sup> and 42.1 kg/m<sup>2</sup>, respectively  $p = 0.076$ . BMI was significantly different in the two groups at the 6 months follow-up ( $p < 0.001$ ) (fig. 1).

### Data at 1 year follow-up

Serum magnesium concentrations increased from 0.77 mmol/L before laparoscopic sleeve gastrectomy surgery to 0.86 mmol/L at the 1-year follow-up ( $p < 0.001$ ) and decreased 0.78 to 0.73 mmol/L in the control group ( $p = 0.002$ ). The intergroup difference regarding serum magnesium at the 1-year follow-up was statistically significant ( $p < 0.001$ ) (fig. 2).

In the experimental group, the mean BMI decreased from 43.2 kg/m<sup>2</sup> at baseline to 30.1 kg/m<sup>2</sup>, after 1 year ( $p < 0.001$ ). In the control group, a small change but again non-significant in mean BMI was observed between baseline and 1 year follow-up, BMI 42.4 kg/m<sup>2</sup> and 42.3 kg/m<sup>2</sup>, respectively  $p = 0.794$ . BMI was significantly different in the two groups at the 1 year follow-up ( $p < 0.001$ ) (fig. 1).

When we analyzed the difference between the after 6 months and after 1 year data, serum magnesium concentration increased in the experimental group, from 0.82 to 0.86 mmol/L ( $p < 0.001$ ), while an opposite trend was noted during the 6 months period in the control group, from 0.76 to 0.73 mmol/L ( $p = 0.009$ ). The intergroup difference in serum magnesium concentrations at the 6-months follow-up ( $p < 0.001$ ) was significant.

In the experimental group, the mean BMI decreased from 33.2 kg/m<sup>2</sup> at 6 months after the operation to 30.1 kg/m<sup>2</sup>, at 1 year after the operation ( $p < 0.001$ ). In the control group, a small change but non-significant in mean BMI was observed between 6 months after operation and

1 year follow-up, BMI 42.1 kg/m<sup>2</sup> and 42.3 kg/m<sup>2</sup>, respectively ( $p = 0.472$ ). BMI was significantly different in the two groups at the 1 year follow-up ( $p < 0.001$ ).

### Adjusted analyses - ANCOVA

When we controlled the preoperation values, using ANCOVA, the statistical significance difference between control and experimental groups maintained on serum magnesium levels after 6 months ( $p < 0.001$ ), after 12 months ( $p < 0.001$ ) and also for BMI 6 months post operation ( $p < 0.001$ ) and BMI 12 months post operation ( $p < 0.001$ ).

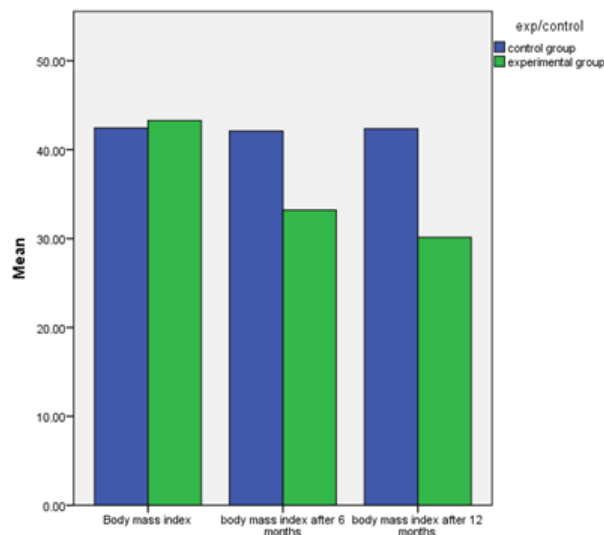


Fig. 1. Changes in BMI (kg/m<sup>2</sup>) baseline to 6 month to 1-year follow-up in obese patients treated with laparoscopic sleeve gastrectomy surgery compared to untreated controls

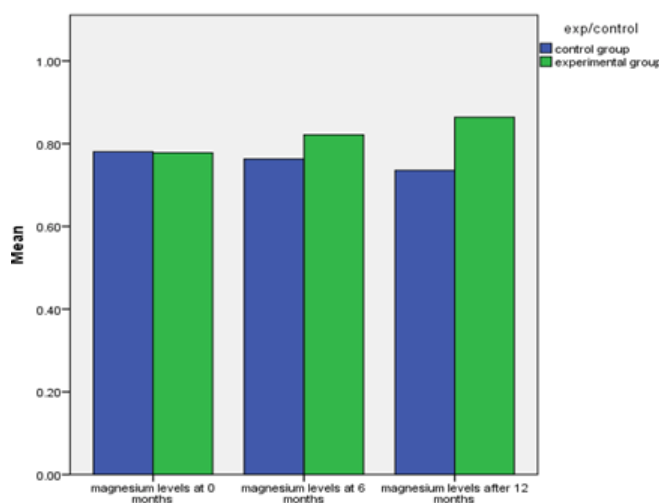


Fig. 2. Changes in serum magnesium (mmol/L) baseline to 6 month to 1-year follow-up in obese patients treated with laparoscopic sleeve gastrectomy surgery compared to untreated controls

In our study, we observed that the serum magnesium concentration increased significantly from 0.77 to 0.82 mmol/L after the first six months and to 0.86 mmol/L during the first year after the laparoscopic sleeve gastrectomy surgery. The increase in serum magnesium was accompanied by an expected major decrease in BMI, from 43.2 kg/m<sup>2</sup> before the operation to 33.2 kg/m<sup>2</sup> after 6 months and to 30.1 kg/m<sup>2</sup> after another 6 months at the 1 year mark after the operation. In the control group no statistical significant difference was observed regarding either the BMI or the serum magnesium level, after 6 months or after 1 year. Although, a non-significant decrease in

serum magnesium levels was observed in the control group from 0.78 mmol/L to 0.76 mmol/L after 6 months and to 0.73 mmol/L after 1 year. It is important to be mentioned that although a significant increase for the experimental group and a non-significant decrease for the control were observed, the values were always in the normal range (between 0.7 and 1 mmol/L). In the literature, the data about potential changes in magnesium levels after bariatric operations is conflicting. For example, we found a study [53] which reported a similar but non-significant increase in serum magnesium concentrations in a reduced sample of only eight obese patients who underwent a bariatric surgery. In another research [54], which studied the potential impact of bariatric surgery on bone metabolism on a larger sample of 110 patients observed that none of the patients showed hypomagnesemia. In a study with an extended period of follow up (5 years), Goode et al. [54] reported normal serum magnesium levels in the experimental group which underwent bariatric surgery, as well as in the control group, which was BMI matched. The authors concluded that the magnesium levels might be associated to the change in BMI per se rather than the method of treatment. A possible explanation of these contradictory results may be that different methods of bariatric surgery might have different effects on the serum magnesium levels because hypomagnesemia has been reported more frequent in patients who underwent jejunoleal bypass for example [55]. These differences are notable although the weight reduction is similar as in the laparoscopic sleeve gastrectomy treated subjects in the present study. Different confound variables such as altered magnesium absorption or induced side effects like diarrhea might help explaining the observed discrepancies between different bariatric surgical methods. The recommended diet regime after laparoscopic sleeve gastrectomy is characterized by a lower calorie intake but with a high content of nutrients. However, the diet is not supplemented with magnesium. Further studies with dietary registration consisting of a food diary should be carried out to determine the exact influence of the post operation diet on magnesium levels.

## Conclusions

To conclude, the patients who underwent laparoscopic sleeve gastrectomy surgery were characterized by an expected BMI decreased and by an increased circulating magnesium level. These findings, may suggest an inverse association between a lower body fat level and an improved magnesium status. However, further detailed investigations are needed to identify the exact underlying mechanisms. Furthermore, the role of magnesium in obesity and comorbid conditions should be established, to answer the question whether or not dietary magnesium deficiency is a significant nutritional concern.

## References

- GALLAGHER, E.J., LEROITH, D., KARNIELI, E., *Med. Clin. North Am.*, **95**, 2011, pp. 855-873.
- GARBER, A.J., *Diabetes Obes. Metab.*, **14**, 2012, pp. 399-408.
- DANAELI, G., FINUCANE, M.M., LU, Y., *Lanc.*, **378**, 2011, pp. 31-40.
- GILCA, G., STEFANESCU, G., BADULESCU, O., TANASE, D.M., BARARU, I., CIOCOIU, M., *Journal of Diabetes Research*, 2017, Article Number: 1310265. DOI: 10.1155/2017/1310265.
- SHAMSEDDEN, H., GETTY, J.Z., HAMDALLAH, I.N., *Surg. Clin. North Am.*, **91**, 2011, pp. 1163-1172.
- TROFIN, F., CIOBICA, A., COJOCARU, D., CHIRAZI, M., HONCERIU, C., TROFIN, L., SERBAN, D., TIMOFTE, D., COJOCARU, S., ANTON, E., *Central European Journal of Med.*, **9**, 2014, pp. 722-728.
- TIMOFTE, D., TOARBA, C., HOGAS, S., COVIC, A., CIOBICA, A., CHIRITA, R., LEFTER, R., ARHIRE, L., ARCAN, O., ALEXINSCHI, O., SERBAN, D., GRAUR, M., POROCH, V., *Romanian Biotechnological Lett.*, **21**, 2016, pp. 11246-11253.
- ANTON, E., ROTARU, A., COVATARIU, D., CIOBICA, A., TIMOFTE, D., POPESCU, R., ANTON, C., *Archives of Biological Sci.*, **67**, 2015, pp. 895-897.
- TROFIN, F., CIOBICA, A., HONCERIU, C., COJOCARU, S., STOICA, B., COJOCARU, D., CIORNEA, E., TIMOFTE, D., *Romanian Biotechnological Lett.*, **22**, 2017, pp. 12439-12447.
- PADURARIU, M., PREPELITA, R., CIOBICA, A., DOBRIN, R., TIMOFTE, D., STEFANESCU, C., CHIRITA, R., *Neurophysiol.*, **48**, 2016, pp. 312-321.
- TIMOFTE, D., LIVADARIU, R., BINTINTAN, V., DIACONU, C., IONESCU, L., SANDBERG, A.A., MARICIUC, D.C., DANILA, R., *Rev Med Chir Soc Med Nat Iasi.*, **118**, 2014, pp. 392-398.
- RUBINO, F., KAPLAN, L.M., SCHAUER, P.R., *Ann. Surg.*, **251**, 2010, pp. 399-405.
- CUMMINGS, D.E., OVERDUIN, J., FOSTER-SCHUBERT, K.E., *Surg. Obes. Relat. Dis.*, **1**, 2007, pp. 109-115.
- \*\*\* OECD, *Health at a Glance: Europe 2014 completed with Eurostat Statistics Database*, OECD Publishing, 2014.
- WORLD HEALTH ORGANIZATION, *Global status report on noncommunicable diseases attaining the nine global noncommunicable diseases targets; a shared responsibility*, 2014.
- CINTEZA, M., PANA, B., COCHINO, E., *Mædica J. Clin. Med.*, **2**, 2007, pp. 277-282.
- DOROBANTU, M., BADILA, E., GHIORGHE, S., *Rom. J. Intern. Med.*, **46**, 2008, pp. 29-37.
- HAGLIN, L., TORNKVIST, B., BACKMAN, L., *Acta Diabetol.*, **44**, 2007, pp. 138-43.
- JORGENSEN, S., OLESEN, M., GUDMAN-HOYER, E., *Scand. J. Gastroenterol.*, **32**, 1997, pp. 334-339.
- BLOOMBERG, R.D., FLEISMAN, A., NALLE, J.E., *Obes. Surg.*, **15**, 2005, pp. 145-54.
- Food and Agriculture Organization/World Health Organization, *Vitamin and Mineral Requirements in Human Nutrition*, 2nd ed. Geneva: Food and Agriculture Organization/ World Health Organization, **1**, 2004, pp. 217-228.
- Food and Nutrition Board, Institute of Medicine, *Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride*. Washington DC: National Academy Press, **1**, 1997, pp. 190-249.
- MOSHFEGH, A., GOLDMAN, J., AHUJA, J., RODES, D., LACOMB, R., *What We Eat in America, NHANES 2005-2006: Usual Nutrient Intakes from Food and Water Compared to 1997 Dietary Reference Intakes for Vitamin D, Calcium, Phosphorus, and Magnesium*. US Department of Agriculture, Agricultural Research Service, 2009.
- MA, J., FOLSOM, A.R., MELNICK, S.L., *J. Clin. Epidemiol.*, **48**, 1995, pp. 927-940.
- ABBOTT, R.D., ANDO, F., MASAKI, K.H., *Am. J. Cardiol.*, **92**, 2003, pp. 665-669.
- TOUYZ, R.M., *Mol. Aspects. Med.*, **24**, 2003, pp. 107-136.
- RUDE, R.K., SINGER, F.R., GRUBER, H.E., *J. Am. Coll. Nutr.*, **28**, 2009, pp. 131-141.
- BARBAGALLO, M., DOMINGUEZ, L.J., GALIOTO, A., *Mol. Aspects. Med.*, **24**, 2003, pp. 39-52.
- BALMUS, I., STRUNGARU, S., CIOBICA, A., NICOARA, M., DOBRIN, R., PLAVAN, G., STEFANESCU, C., *Oxidative Medicine and Cellular Longev.*, **1**, 2017, pp. 1-7. doi.org/10.1155/2017/7156928.
- BALMUS, I., CIOBICA, A., ANTIOCH, I., DOBRIN, R., TIMOFTE, T., *Oxidative Medicine and Cellular Longev.*, **1**, 2016, pp. 1-25. doi.org/10.1155/2016/3975101.
- CIOBICA, A., PADURARIU, M., CIOBICA, A., TIMOFTE, D., STEFANESCU, C., NASREDDINE, Z., *International Journal of Geriatric Psychiatry.*, **32**, 2017, pp.116-117.
- ANTIOCH, I., CIOBICA, A., PAULET, M., BILD, V., LEFTER, R., TIMOFTE, D., *Psychiatr. Danub.*, **27**, 2015, pp. 142-152.

32. DAI, Q., SHRUBSOLE, M.J., NESS, R.M., *Am. J. Clin. Nutr.*, **86**, 200, pp. 743-751.
33. LEONE, N., COURBON, D., DUCIMETIERE, P., ZUREIK, M., *Epidemiology*, **17**, 2006, pp. 308-314.
34. RIDKER, P.M., *Nutr. Rev.*, **65**, 2007, pp. 253-259.
35. KING, D.E., MAINOUS, A.G. III, GEESEY, M.E., ELLIS, T., *Magnes. Res.*, **20**, 2007, pp. 32-36.
36. KING, D.E., MAINOUS, A.G. III, GEESEY, M.E., WOOLSON, R.F., *J. Am. Coll. Nutr.*, **24**, 2005, pp. 166-171.
37. RODRIGUEZ MORAN, M., GUERRERO ROMERO, F., *Magnes. Res.*, **17**, 2004, pp. 189-196.
38. CORICA, F., ALLEGRA, A., IENTILE, R., BUEMI, M., *Am. J. Hypertens.*, **10**, 1997, pp. 1311-1313.
39. LEE, S., PARK, H.K., SON, S.P., LEE, C.W., KIM, L.J., KIM, H.J., *Nutr. Metab. Cardiovasc. Dis.*, **19**, 2009, pp. 781- 788.
40. HUERTA, M.G., ROEMMICH, J.N., KINGTON, M.L., *Diabetes Care.*, **28**, 2005, pp. 1175-1181.
41. CORICA, F., ALLEGRA, A., IENTILE, R., *Am. J. Hypertens.*, **12**, 1999, pp. 128-136.
42. AGHEORGHIESEI CORODEANU, D.T., POROCH, V., A possible theoretical model of ethical system management in healthcare institutions, 6th LUMEN International Conference on Rethinking Social Action Core Values, 16-19 April 2015, Iasi, Romania, Rethinking Social Action. Core Values, p. 33-41.
43. TOADER, E., TOADER, T., *Revista Romana de Bioetica*, **10**, no. 3, 2012, p. 66.
44. TOADER, E., *Revista Romana de Bioetica*, **8**, no. 2, 2010, p. 157.
45. BALAN, G.G., TRIFAN, A., SAVIN, C., BALAN, A., GOLOGAN, E., *Revista de Cercetare si Interventie Sociala*, **55**, 2016, pp. 244-259.
46. BALAN, G.G., MITRICA, D.E., IACOB, M., BALAN, A., ZETU, I., *Revista de Cercetare si Interventie Sociala*, **49**, 2015, pp. 229-238.
47. BALAN, A., SAVIN, C., BALAN, G.G., ZETU, I., *Revista de Cercetare si Interventie Sociala*, **45**, 2014, pp. 160-174.
48. TOADER, E., *Revista de Cercetare si Interventie Sociala*, **37**, 2012, p. 144.
49. CHIRITA, P., ASAFTEL I.V., SANDU, I., SARBU, L.G., LUPU, V.V., *Rev. Chim. (Bucharest)*, **68**, no. 1, 2017, p. 147
50. PAVEL, S., HOPF, H., JONES, P.G., LUPU, V.V., BIRSA, L.M., *Rev. Chim. (Bucharest)*, **67**, no. 4, 2016, pp. 683-686.
51. CANTEMIR, A., ALEXA, A.I., CIOBICA, A., TOADER, E., BALMUS, I.M., COJOCARU, S.I., CHISELITA, D., COSTIN, D., *Rev.Chim. (Bucharest)*, **67**, no. 9, 2016, p. 1725
52. VAN GAAL, L., DELVIGNE, C., VANDEWOUDE, M., *J. Am. Coll. Nutr.*, **5**, 1987, pp. 397-400.
53. DINIZ, F., DINIZ, M.T., SANCHES, S.R., *Obes. Surg.*, **14**, 2004, pp. 1222-1226.
54. GOODE, L.R., BROLIN, R.E., CHOWDHURY, H.A., *Obes. Res.*, **12**, 2004, pp. 40-47.
55. SINGH, D., LAYA, A.S., ALLEN, M.J., CLARKSTON, W.K., *World J. Gastroenterol.*, **15**, 2009, pp. 2277-2279.

---

Manuscript received: 21.02.2017