“CAROL DAVILA” UNIVERSITY OF MEDICINE AND PHARMACY

BUCHAREST

DOCTORAL SCHOOL

FIELD OF MEDICINE

Gastric sleeve impact on the relationship between body composition parameters, adipokines, and bone metabolism in patients with obesity

ABSTRACT OF DOCTORAL THESIS

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YEAR 2023

CONTENT

INTRODUCTION

Obesity is a complex pathology, with a continuously increasing prevalence, reaching pandemic proportions in recent decades. Thus, this area has a relevant theme both from a medical and social point of view, being at the center of an impressive number of scientific studies and, at the same time, influencing public health policy.

Initially, obesity was considered a problem of developed countries. During the time, it has also increased in low- and middle-income countries, especially in urban areas. WHO data on the dynamics of the obesity phenomenon, between 1975 and 2016, show a tripling of the number of people affected. Thus, in 2016, globally, over 1.9 billion adults over the age of 18 were overweight. Of these, more than 650 million adults were known to be obese, representing approximately 13% of the planet's population. This upward trend was also observed among children, with more than 350 million between 5-19 years being overweight or already diagnosed with obesity. Also, from the data reported to the WHO, it follows that the USA and Saudi Arabia have the highest recorded rates of obesity, over 35%. Data related to Romania showed, in 2016, a percentage of 57.7% of the adult population as overweight and 20-29.9% with obesity (WHO, 2021).

From the point of view of the economic impact, WHO forecasts show that by 2035 more than half of the planet's population will be affected by overweight or obesity. This means a value of more than 4.32 trillion dollars annually (i.e. 3% of the global GDP).), if prevention and control measures do not improve significantly. This effect is comparable to that of COVID-19, in the year 2020 (Lobstein et al., 2023).

Obesity's numerous complications are well known and have been extensively researched. As BMI is not very accurate in assessing adipose tissue distribution and predicting metabolic risk (Tomiyama et al., 2016), some alternative ways have been developed to identify more accurately these parameters. Dual-energy X-ray absorptiometry (DXA) is a technique used in the assessment of bone mineral density and the diagnosis of osteoporosis. This technique has also been shown to be effective and useful in assessing body composition to determine the amount of fat mass and lean mass (Laskey, 1996).

The studies that have been performed so far indicate that the distribution of the adipose tissue is more important than its quantity. The accumulation of adipose tissue in the abdominal region is associated with an increased risk of comorbidities and even mortality, while an increased hip circumference is associated with a decreased cardiovascular risk (Snijder et al., 2004).

Adipose tissue is a tissue composed mainly of adipocytes, being recognized as the largest endocrine organ of the body. It secretes several factors, including adipokines (Zorena et al., 2020). Adipokines are involved in the control of satiety and appetite, adipose tissue distribution, insulin secretion and sensitivity, endothelial function, inflammation, homeostasis and in bone metabolism (Fasshauer and Blüher, 2015). Among these adipokines it can be found also adiponectin, which has an anti-inflammatory role and regulating insulin sensitivity. In addition, adiponectin receptors have been identified on osteoblasts and osteoclasts, which is why it has been proposed as a mediator between bone and adipose tissue (Naot, Musson and Cornish, 2017).

The link between adipose tissue and bone metabolism is more debatable. It is interesting how literature assigns obesity both a positive and a negative role The interaction between bone and adipose tissue was initially studied with an emphasis on mechanical stress (bone mechanical loading), but as research progressed, a two-way communication, via cytokines and hormones, between adipose tissue and bone has been described. Data are suggesting that adiponectin increases bone mass by inhibiting osteoclastogenesis and bone resorption at the level of osteoclasts (Oshima et al., 2005); other studies showed a negative effect on bone formation due to stimulation of RANKL, which drives bone resorption, and by inhibiting osteoprotegerin production by osteoblasts (Brzozowska et al., 2013).

Ten years ago, gastric sleeve started to be mentioned in guidelines as an established bariatric surgery procedure, surpassing the status of an investigational procedure, as it was considered before 2013 (Mechanick et al., 2013). Since then, it has gained more and more popularity, in the year 2020. The American Society for Bariatric and Metabolic Surgery reported that a percentage of 61% of bariatric procedures were represented by the gastric sleeve (ASMBS, 2021).

THE STARTING HYPOTHESIS OF THE STUDY

Although the beneficial effects of bariatric surgery are clear, studying and managing the negative side effects on bone metabolism continue to be a challenge. A major research concern in this field is represented by the characterization of bone structural changes. The altered bone metabolism, the accelerated bone loss, and the increased fracture risk have been reported in patients undergoing RYGB, while data on the impact of SG on bone are still scarce (Johnson et al., 2005; Ko et al., 2016; Liu et al. ., 2016).

An increase in bone resorption occurs as early as the first postoperative weeks, with a maximum reached at 6-12 months (Muschitz et al., 2015; Yu et al., 2016). Still, much of the research done is on patients undergoing RYGB, but a few studies compare the effects of RYGB vs. SG on the bone. The results are different, but in most of them RYGB seems to have a greater decrease in BMD (Carrasco et al., 2014; Hsin et al., 2015; Muschitz et al., 2015). This bone loss is related to several factors including: decreased mechanical loading, nutritional deficiencies, hormonal changes and physical activity (Shahraki et al., 2022). However, few studies to date have evaluated the relationship between adipokines and markers of bone turnover in patients undergoing bariatric surgery.

THE SCIENTIFIC OBJECTIVES

My interest in this doctoral research topic arose out of a desire to gain a better understanding both on how weight loss occurs by body region and on the factors that underlie bone loss. I also aimed to deepen the relationship between adiposity and bone, trying to identify the effect of the gastric sleeve intervention on changes in adiponectin and bone markers. Last but not least, I set out to identify some links that are the basis of this complex relationship. The research focuses on several directions, which are embodied in the following four studies:

In the first study, I aimed to evaluate the general characteristics of obese patients and the results of the gastric sleeve intervention from the point of view of efficiency regarding weight loss, improvement of metabolic complications, but also changes in the parameters of phospho-calcium metabolism.

In the second study, I proposed the following categories of measurements and scientific interpretations:

• evaluation of changes in body composition after 6 and, subsequently, at 12 months after gastric sleeve surgery.

• analysing the evolution of bone mineral density after gastric sleeve surgery.

• analysing the impact of body composition parameters on bone mineral density.

In the third study, I focused on the following types of scientific investigations:

• evaluation of changes in adiponectin and bone turnover after 6 months and, subsequently, after 12 months after gastric sleeve surgery.

• identifying the relationship between adiponectin and body composition parameters, as well as factors involved in adiponectin changes after gastric sleeve surgery.

• identifying the relationship between bone metabolism with adiponectin and body composition parameters

In the fourth study, I set out to study the following:

• weight dynamics through the evaluation of weight recovery after the minimum weight reached and the identification of factors that influence long-term weight regain.

• the evolution of body composition parameters 4 years after gastric sleeve surgery.

• evolution of bone mineral density 4 years after gastric sleeve surgery and the influence of body composition changes on bone.

RESEARCH METHODOLOGY

The studies that are included in this doctoral thesis started from a database in which I included 323 patients with obesity, who performed the gastric sleeve intervention and who were evaluated within a multidisciplinary project, in collaboration with a team of specialized doctors on bariatric surgery from the "Center of Excellence in Bariatric Surgery" within the "Ponderas" Hospital. Patients who met the criteria for bariatric surgery according to the guidelines were included in the study, respectively: a) patients with BMI ≥ 40 kg/m2 or BMI ≥ 35-40kg/m2 plus comorbidities associated with obesity (type 2 diabetes, hypertension, dyslipidemia, sleep apnea syndrome, steatosis or non-alcoholic steatohepatitis, osteoarthritis, chronic venous insufficiency or other diseases affecting the quality of life); b) patients with BMI ≥ 30-35 kg/m2 plus type 2 diabetes and/or hypertension uncontrolled by optimal treatment. The exclusion criteria were represented by pre-existing bone pathologies (osteoporosis, chronic treatment with drugs that affect bone metabolism), the presence of muscle disorders, prolonged immobilization in bed, age under 18 years or over 70 years, people who wear metal implants, prostheses orthopedic devices or cardiac pacemaker because they can influence the result of osteodensitometry.

The patients were monitored by a multidisciplinary team. The evaluation included cardiac, pulmonary, endocrinological/diabetological, psychological and nutritional parameters. They were instructed to make healthy food choices before surgery. According to the current guidelines, the patients were recommended to supplement with bariatric vitamins and multiminerals (including vitamin D and calcium).

The evaluation was carried out through anamnesis, clinical examination with measurement of anthropometric parameters, laboratory investigations and paraclinical investigations (DXA whole body and abdominal ultrasound). All assessments were performed preoperatively, 6 and 12 months postoperatively.

- Dual X-ray absorptiometry (DXA) whole body:

It was used to assess bone mineral density (BMD) and body composition analysis. The machine on which the measurements were performed was the Lunar iDXA (GE Healthcare). Both total and regional amounts of adipose tissue (FM) and lean mass (LM) on each limb and trunk were assessed.

The adipose tissue parameters used were: total fat mass (TFM), gynoid fat mass (GFM), android (AFM), upper and lower limbs; body fat percentage (BFM %), Android/Gynoid ratio (A/G), visceral adipose tissue (VAT)

The muscle tissue parameters used were: total lean mass (TLM), gynoid lean mass (GLM), android (ALM), upper and lower limb (ASM), lean mass percentage (TLM %), appendicular skeletal muscle mass index (ASMI - which is the sum of the lean mass of the upper and lower limbs divided by the square of the height)

Bone tissue parameters: total bone mineral density (BMD - g/cm2), regional bone mineral density (limbs, spine, trunk, ribs, pelvis, head), bone mineral content (BMC - g), body T score (T score total body), Z score at the body level (Z score total body)

Patients' follow-up after gastric sleeve:

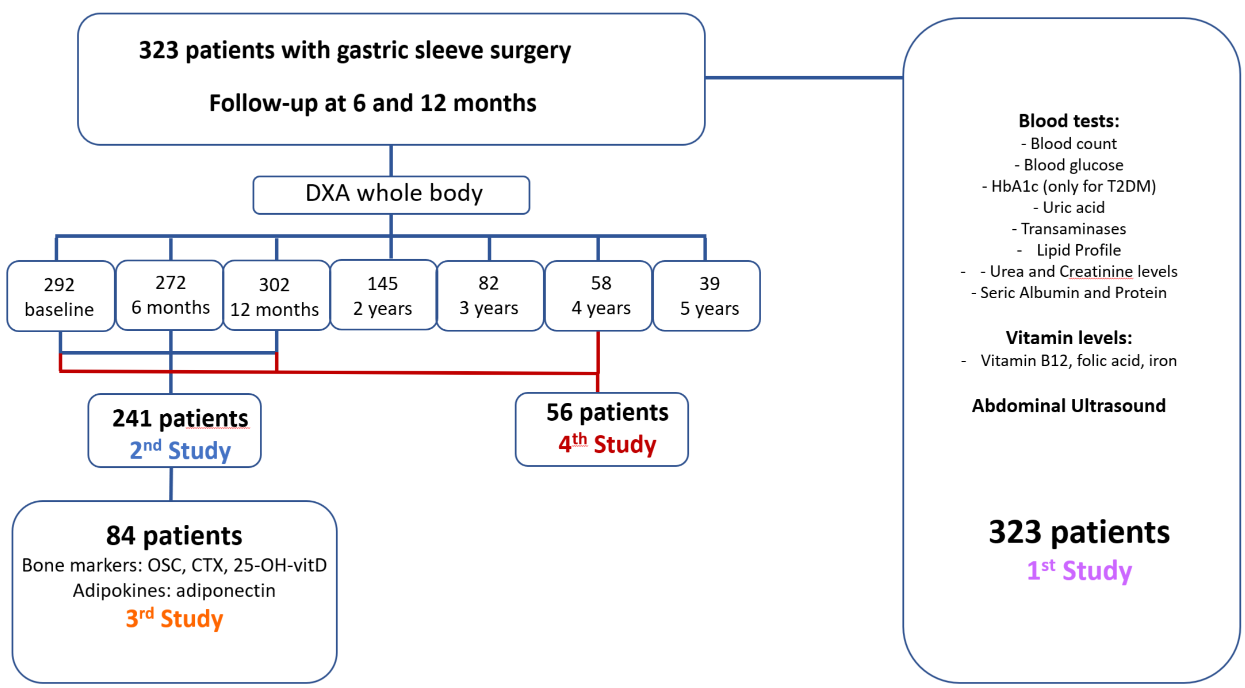
Excess weight loss was assesed acording to the following formula, assuming a normal BMI of 25 kg/m^2 (Deitel & Greenstein, 2003):

%EWL= [(Baseline BMI- Current BMI)/(Baseline BMI-25)]*100

Changes in clinical and biological parameters were evaluated both as an absolute change and as a percentage change according to the formula:

Variation of x (%)= [(Baseline x level – Postoperative x level)/(Baseline x level)]*100

STUDY DESIGN:



Statistical analysis was performed using SPSS software, version 23.0 for Windows (SPSS Inc Chicago IL).

1st Study – Evolution at 6 and 12 months after bariatric surgery regarding clinical and biological characteristics of patients with obesity

We evaluated 323 patients: 133 (41.18%) men and 190 (58.82%) women. Age ranged from 18-68 years with a mean age of 41.62±11.04 years and no significant difference between genders. The duration of obesity had a median of 15 years (IQR 15; range: 1–52 years) with no significant differences between genders, and a number of 112 patients (34.67%) were diagnosed with obesity before reaching the age of 18 years.

The greatest weight loss is noted during the first 6 months post-surgery, with a median number of kilograms loss of 35.15 (15.78) kg. During the following 6 months, an average of 8 kg was lost, only 15 of the patients had a slight weight regain (2 kg on average), while 4 patients maintained the same weight from 6 months. Therefore, after a year following the surgery, it had decreased by 43.7 (20) kg. TWL (%) at 12 months was 34.91±7.77 % (35.82±7.71 men and 34.27±7.76% women). Additionally, we observed that 218 patients (67.49%) had a BMI below 30 kg/m2 at 12 months after surgery, meaning they no longer met the criteria for the diagnosis of obesity.

We also evaluated weight loss through the perspective of EWL (%- Excess weight loss percentage), which achieved a value of 69.33 (24.09%) at 6 months and 84.70 (29.10) at 12 months. Using logistic regression analysis and ROC curve we found that young individuals with a lower BMI had a greater EWL (Fig. 1)

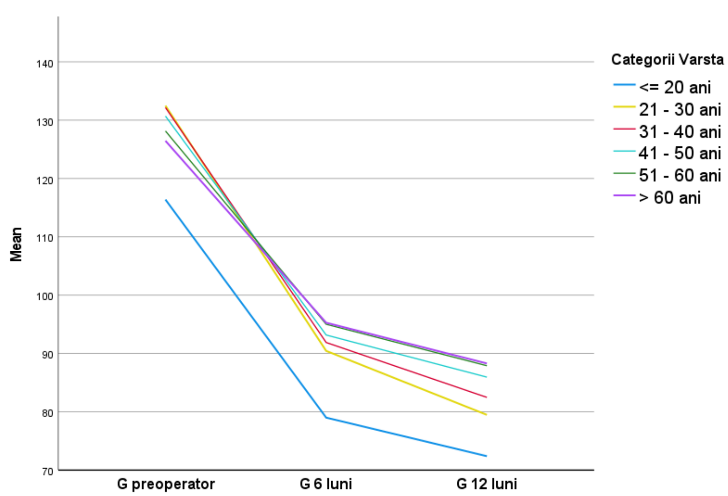


Fig 1- Age distribution by decade and weight evolution at 6 and 12 months after SG

Improvement in chronic complications of obesity has been observed:

- Type 2 diabetes had a complete remission for 63.2% of patients and a partial remission for 13.2% of patients.
- Hypertension had a prevalence of 49.5% preoperatively, and 12 months postoperatively only 15.2% remained with antihypertensive treatment.
- Hepatic steatosis improved for all patients 12 months after the gastric sleeve, and for 34.4% of them, it went into remission; liver function was improved by 26.2% in AST, 51.1% in ALT, and 53.13% in GGT.
- We found that after 12 months the value of total cholesterol decreased by 6.84%, while HDL-Cholesterol increased by 9.71%, and triglycerides improved by 39.78%.

To evaluate changes in bone metabolism before and after SG, total serum calcium and PTH levels were measured for nearly every person in the study group. In addition, we analyzed 25-OH-vitamin D, osteocalcin, and CTX for 84 individuals.

PTH had values that exceeded the upper limit for only 2.4% of patients preoperatively, 2.3% had higher values at 6 months, while at 12 months the percentage was only 2%.

60.7% of patients had a preoperative vitamin D deficiency (<20 ng/mL), and after 12 months the percentage decreased to 21.7% (no patient had a value lower than 12 ng/mL). There was no statistically significant difference between men and women regarding these parameters.

Vitamin D was positively correlated with % EWL at 6 and 12 months (r=0.455, p<0.001 – Fig 2; r=0.344, p<0.001).

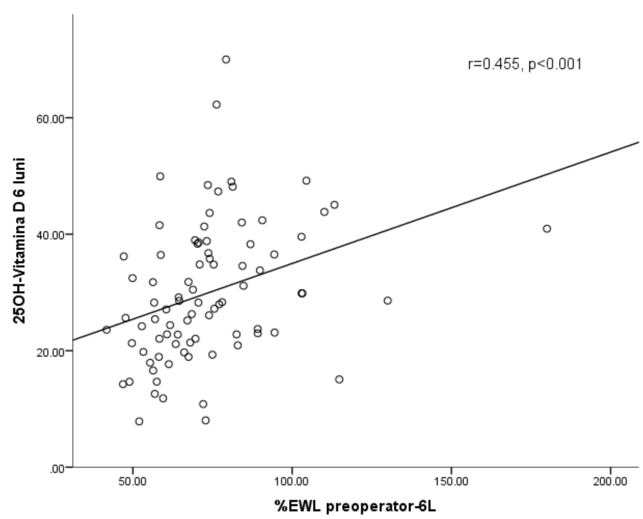


Fig. 2 -Correlation between vitamin D and EWL at 6 months

2^{nd} Study - Body composition changes and bone mineral density variation 6 and 12 months after gastric sleeve

A. Changes in body composition

A total of 241 subjects (140 women (58.1%) and 101 men (41.9%)) were included. DXA scans were performed for all patients; total body and regional values of BMD were evaluated at baseline, 6 and 12 months after gastric sleeve.

12 months after surgery, all parameters related to FM and LM decreased significantly, with a predominantly greater decrease in FM. The decrease percentage of FM after 12 months following SG reached a maximum of 64.2% at the android region, while LM had a decrease of 16.29% at this level; Total FM loss percentage was 55.25% and LM loss reached a percentage of 14.27%. Men had greater variation in fat mass than women, while variation in lean mass was similar between genders.

Basically, a TFM loss of approximately 27.5 kg was achieved in the first 6 months, continuing to decrease by approximately 1.2 kg/month, reaching approximately 35 kg at 12 months. The percentage of fat mass decreased on average by 10.9% in the first 6 months, reaching up to 16.2% at 12 months, with the largest decrease occurring at the android level (of approximately 21%).

The reduction of LM in the upper and lower limbs also led to a significant reduction of the ASMI index which had a decrease of 13.78 ± 8.16% after the first 6 months, reaching 16.2 ± 8.34% at 1 year.

Of the total weight loss, we noted that a percentage of 22% was represented by lean mass at 6 months, with some individual values even reaching 56%. A lower baseline BMI was observed in patients who lost more muscle mass, and android-type obesity (represented by the A/G ratio measured by DXA) along with a higher glycemic value were among the predictors of this loss.

Additionally, I tried to determine the prevalence of sarcopenia, but having as a limitation of the study the lack of measurement of muscle strength, I evaluated the low muscle mass through several formulas proposed by guidelines or important working groups in the evaluation of sarcopenia:

- I have used DXA scans of the NHANES population as a reference and calculated Z score of ASMI (ASM/I2) with a cut-off of -1SD from the mean value specific to sex and age in the reference population.
- I have used the FNIH- recommended criteria by calculating the appendicular lean mass related to BMI (ASM/BMI)
- I calculated the appendicular lean mass related to weight (ASM/G) according to the recommendations of the latest EASO and ESPEN consensus.
- I have used the ASMI index (appendicular lean mass divided by heigh^2) with the thresholds recommended by EWGSOP2, and with those used by Bouchard.

Thus, we observed differences between the formulas and thresholds used. The prevalence of low muscle mass at the preoperative assessment varied between 0 and 92% (for men), 81.4% (for women), at 6 months it varied between 1%-31.7% in men and 0.7%-26.4% in women, and in 12 months between 2%-36.6% in men and 0-11.4% in women.

Although we obtained very different percentages depending on the criterion used, in all cases the prevalence of low lean mass was higher in men, both preoperatively and postoperatively.

B. Bone mineral density changes after gastric sleeve

BMD decreased at almost all analyzed sites at 6 months post-LSG and continued to decline during the subsequent 6 months. Total BMD followed the same downward trend (1.220g/cm2 at 12 months vs 1.292g/cm2 at baseline, $p<0.001$) (Table 1). BMD and BMI decline correlated positively at 12 months ($r=0.134$, $p<0.05$).

Table 1. Densitometric variables at baseline, 6 and 12 months of follow-up

Head BMD (g/cm2)	2.201 ± 0.28	2.190 ± 0.27	2.185 ± 0.27[*b]
Arms BMD (g/cm2)	0.977 ± 0.14	0.937 ± 0.15[a]	0.926 ± 0.14[b]
Legs BMD (g/cm2)	1.344 ± 0.15	1.349 ± 0.14	1.328 ± 0.14[b,c]
Trunk BMD (g/cm2)	1.117 ± 0.11	1.086 ± 0.11[a]	1.058 ± 0.11[b,c]
Ribs BMD (g/cm2)	1.025 ± 0.11	0.960 ± 0.09[a]	0.924 ± 0.10[b,c]
Pelvis BMD (g/cm2)	1.113 ± 0.13	1.105 ± 0.13[*a]	1.079 ± 0.13[b,c]
Spine BMD (g/cm2)	1.277 ± 0.15	1.244 ± 0.13[a]	1.220 ± 0.13[b,c]
Total BMD (g/cm2)	1.292 ± 0.11	1.272 ± 0.11[a]	1.254 ± 0.11[b,c]
Total BMD (g/cm2)	1.292 ± 0.11	1.272 ± 0.11[a]	1.254 ± 0.11[b,c]

[a] - p<0.001 6 months vs baseline [*a] p<0.05 6 months vs baseline
[b]- p<0.001 12 months vs baseline [*b] p<0.05 12 months vs baseline; [c]- p<0.001 12 months vs 6 months

Gender-oriented analysis revealed a more significant bone loss in males at almost all measured sites.

Furthermore, we divided females according to menopausal status (premenopausal N=97, postmenopausal N=43). At 12 months post-LSG, men showed a significantly higher decline in total BMD than premenopausal women at all sites except the head.

To eliminate the impact of confounding factors, we adjusted the analysis for age and BMI change. GLM confirmed a greater total BMD decline in men versus premenopausal women (mean difference 2.37%, $p<0.05$). Conversely, the difference in BMD decline between men and postmenopausal women did not reach statistical significance (Fig. 1).

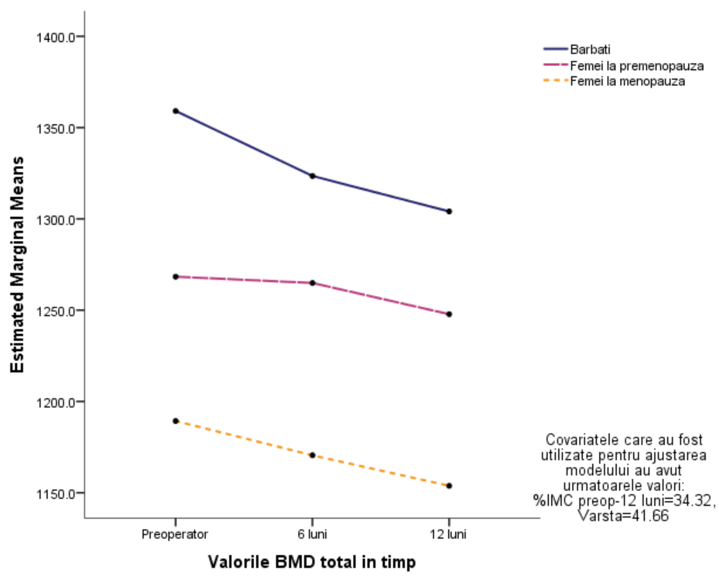


Fig. 3 - Total BMD trends over 12 months adjusted by age and BMI variation. Covariates appearing in the model are evaluated at the following values: %BMI baseline-12months=34.32, age=41.66

C. The relationship between body composition and bone mineral density

I have also assessed the association between body composition parameters and BMD. I identified positive correlations between BMD and lean mass parameters (TLM, percentage of TLM, ASMI) at each measurement, pre- and post-operatively. In addition, I observed negative correlations between BMD and fat mass parameters (total fat mass, percent fat mass and VAT) when adjusted for total weight or BMI. Similar connections between total BMC and body composition parameters were found as well.

In addition, I noticed a positive correlation between the 12-month variations of the total BMC and ASMI (r=0.317, p less than 0.05), variation that remained an independent predictor of bone loss after the linear regression analysis.

3rd Study – Changes in adiponectin and bone markers after gastric sleeve surgery, and their relationship with body composition parameters

A. Adiponectin relationship with anthropometric, metabolic and body composition parameters

From the initial study group of 323 patients evaluated in the first study, we included in this study 84 patients whose levels of adiponectin, bone markers (osteocalcin, CTX) and 25-OH-vitamin D were measured. In addition, I calculated the OSC/ CTX ratio to observe how bone formation and resorption varies after bariatric surgery.

At baseline, adiponectin levels were statistically significantly higher in women than in men. I observed negative correlations with the number of years of obesity, weight, abdominal circumference, waist/hip ratio, waist/height ratio, creatinine, and transaminase levels.

At the same time, after adjusting for age and sex, the adiponectin level correlated positively with the values of 25-OH-vitamin D ($r=0.291$, $p<0.01$), with the osteocalcin level ($r=0.266$, $p<0.05$) and with the OSC/CTX ratio ($r=0.279$, $p<0.05$). I did not observe a correlation between adiponectin values and those of CTX.

I tried to demonstrate the relationship between adiponectin, fat mass and lean mass, total and regional, after complex adjustment for sex, age, creatinine level and body weight. The following results were obtained:

- adiponectin remained negatively correlated with android fat mass while being positively correlated with gynoid fat mass
- adiponectin level remained negatively correlated with android lean mass and gynoid lean mass.
- total fat mass (g) and relative fat mass (%) did not maintain correlation with adiponectin after this complex adjustment.

In a linear regression model in which I introduced all parameters previously shown to correlate with serum adiponectin level, using the stepwise method, age, 25-OH-vitamin D level, osteocalcin and gynoid fat mass (Fig. 5) remained positive predictors, while serum creatinine and android fat mass (Fig. 4) remained negative predictors, all meeting the level of statistical significance. In its complexity, this regression model explains almost 55% of the variation in serum adiponectin.

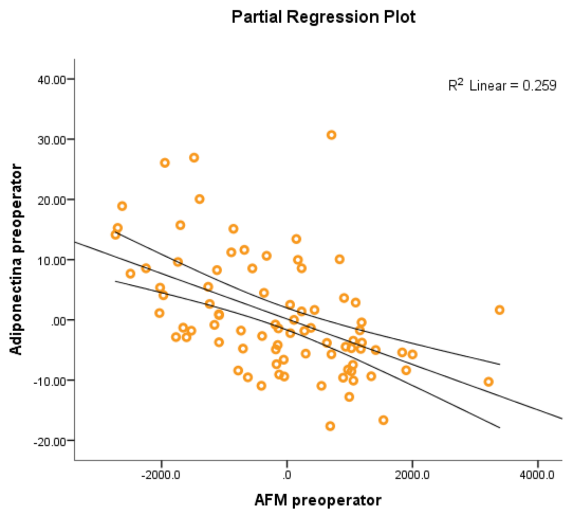


Fig 4 – Partial regression plot between adiponectin and AFM at baseline

Fig 5 - Partial regression plot between adiponectin and GFM at baseline

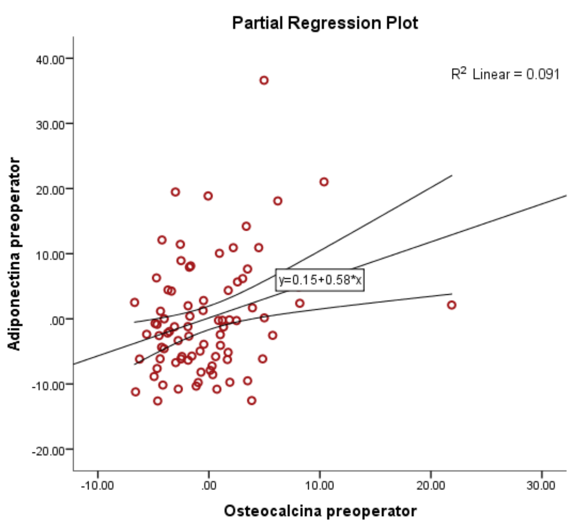


Fig 6 - Partial regression plot between adiponectin and osteocalcin at baseline

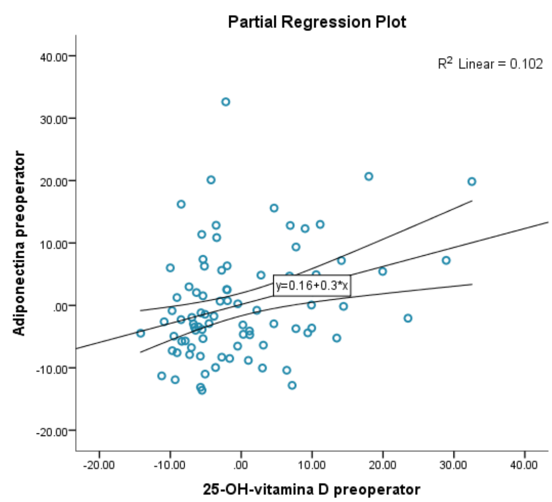


Fig 7 - Partial regression plot between adiponectin 25-OH-vitamin D at baseline

The link between adipose tissue and bone mass is known, and the relationship lies not only in the response to mechanical loading, but also in the communication between the two compartments through hormones and cytokines. Although obesity is associated with low levels of both vitamin D and adiponectin, the connection between them is still not well established. In our patients, as illustrated in figure 6 and figure 7, I identified a relationship between adiponectin and bone through osteocalcin, respectively 25-OH-vitamin D.

B. Adiponectin changes after bariatric surgery

I detected, as expected, increases in adiponectin levels after gastric sleeve.

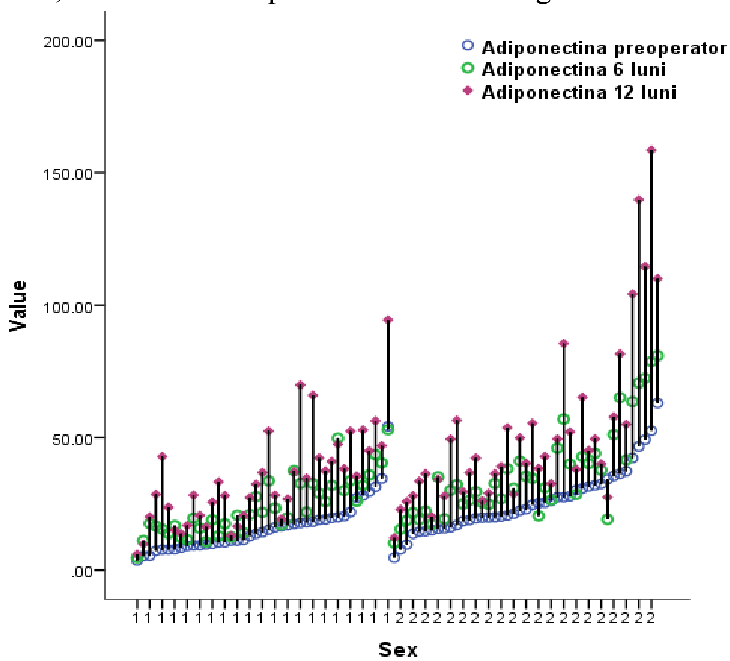


Fig. 8 Adiponectin variation at 6 and 12 months after gastric sleeve

At both 6 and 12 months, the relationships between serum adiponectin levels and Vitamin D, osteocalcin, android and gynoid fat mass were maintained in the same direction as at baseline.

Moreover, I identified that preoperative–12-month variation in android fat mass was an independent predictor of adiponectin variation (a regression model that explained 28% of postoperative adiponectin changes); basically, the more android adiposity decreased, the more adiponectin levels increased.

C. **Bone parameters changes after gastric sleeve and their relationship with metabolic factor, adipokines and body composition**

An increase in bone markers was recorded after gastric sleeve as follows: CTX reached its maximum value at 6 months after surgery (an increase of about 185%), while osteocalcin had a slower increase, reaching its maximum value at 12 months (130% variation).

Marker variations were similar between gender, but a slightly higher CTX value was recorded among men at 6 and 12 months.

Additionally, I analyzed the OSC/CTX ratio and its variation to determine how bone formation varies compared to bone resorption. In the first 6 months after the gastric sleeve, an increase in bone resorption was observed, with the ratio decreasing by approximately 26%; over the next 6 months, the OSC/CTX ratio tended to return to baseline, but there was still a statistically significant decrease of approximately 5% from the preoperative time point (Fig. 9). There were no statistically significant differences in the variation of the ratio between males and females.

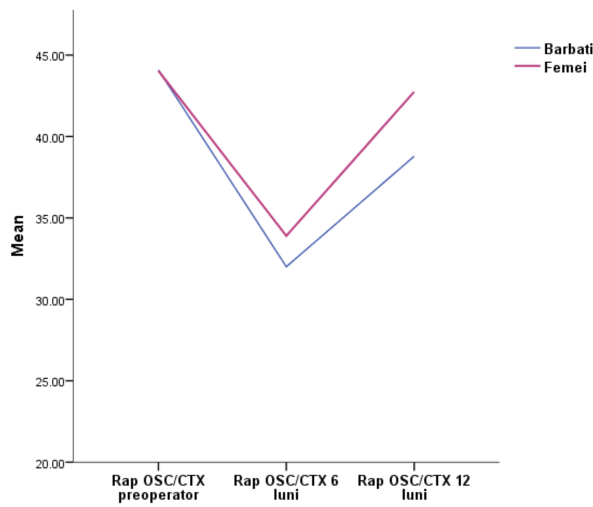


Fig. 9 – Changes in OSC/CTX ratio at 6 and 12 months after gastric sleeve

As expected, CTX and osteocalcin values at 12 months correlated with e variation of total BMD baseline-12months (r=0.245 and r=0.316, respectively, $p<0.05$).

At 12 months postoperatively, the increase in adiponectin (represented by ΔAdiponectin 12months-baseline) was a positive, independent contributing factor in the increase in osteocalcin (represented by ΔOsteocalcin 12L-preoperative), relationship represented in table 2, where Δ=postoperative level- baseline level.

Table 2. Multiple linear regression analysis to determine factors that have an influence on the osteocalcin change at 12 months after gastric sleeve

Dependent variable	Variables	β model	P value
ΔOsteocalcin 12months- baseline **(R^2=0.389, p<0.05)**	Constant	-10.838	
	T2DM	-4.263	<0.05
	ΔAdiponectin 12months-baseline	0.093	<0.05
	ΔCTX 12months-baseline	14.617	<0.001
	Gender	0.471	NS
	%ASMI baseline-12 months	0.66	NS
	%BMI baseline-12 months	0.089	NS
	Number of years with obesity	0.32	NS
	Smoker	-0.866	NS

Also, there was a positive correlation (r=495, p0.05) between baseline-12-month variation of total BMD and 12 month-baseline variation of adiponectin, a factor that remained a predictor of BMD change independent of age, preoperative BMI, vitamin D level, and 12-month-baseline osteocalcin variation.

4th Study - Weight and body composition parameters change over a 4-year period after gastric sleeve

Only the patients whose DXA assessment was completed preoperatively, 1 year, and 4 years after gastric sleeve were chosen for this analysis from the 323 patients who received the SG operation, as assessed in the first study. 56 patients were included in the study. Of these, 46 of them also had DXA assessment at 6 months.

I classified the patients based on weight regain since there were detected disparities in their individual evolution in terms of retaining the minimum weight they obtained. For this, the nadir weight was first determined (the lowest weight attained by the patients) by considering the beginning weight values at 12 months and 4 years, and if the evaluation from 6 was also available on Monday, I also considered this.

Weight regain was calculated using the following formulas:

- ΔWR (kg) = Weight at 4 years (kg) – Nadir weight (kg), where WR= weight regain
- WR (%) = [Weight at 4 years (kg) – Nadir weight (kg)]/Nadir weight (kg)*100

The greatest weight loss in the study group occurred after a year following the gastric sleeve, but it could not be maintained up to 4 years. Thus, while lean mass continued to decline, there was an increase in weight that seemed to be only in total and visceral adipose tissue. Regarding bone mineral density, a decreasing trend has been observed that continues for up to 4 years. In terms of bone mineral density, a decreasing trend has been observed that continues for up to 4 years, with values for nearly all the regions evaluated being significantly lower at 4 years compared to those at 1 year.

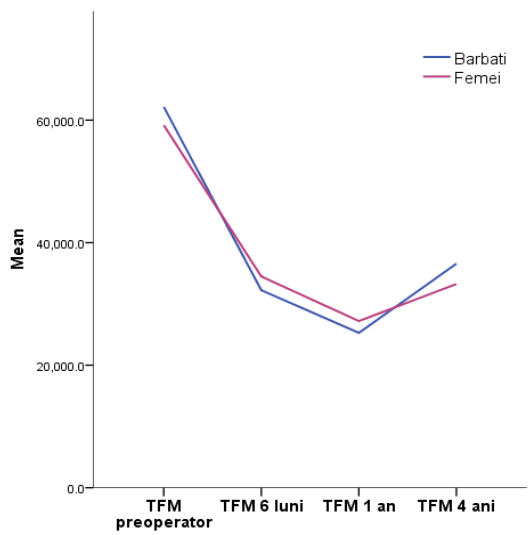


Fig 10 – TFM evolution at 4 year

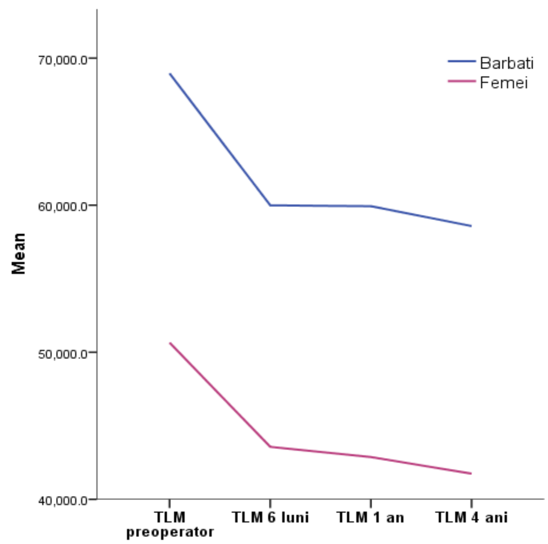


Fig. 11 TLM evolution at 4 year

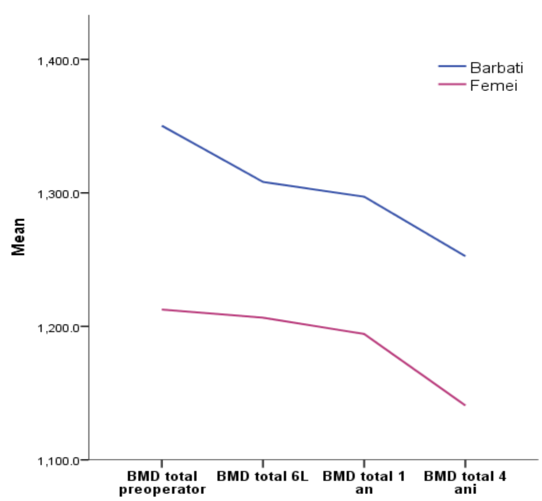


Fig. 12 – BMD evolution at 4 year

The correlation between BMD and ASMI was maintained at 4 years (r=483, p<0.001) even after adjusting for age and sex, and the variation in % BMD 1 year -4 years was positively correlated with the variation in % ASMI 1 year - 4 years (r=446, p<0.001). Through a linear regression model, we identified age, ASMI variation 1 year-4 years and PTH value at 1 year as independent (positive) predictors and explaining approximately 30% of the BMD variation between 1 year and 4 years.

At four years, 10 of the patients had maintained their minimum weight. The greatest weight regain among the others who gained weight was 29.3 kg, and the median WR(%) was 9.15%. I considered a significant weight gain when the percentage change between the weight at 4 years and the minimum weight was greater than 10% (WR (%) ≥10%). Despite the fact that these patients regained weight, the EWL percentage at 4 years was 64.62%, indicating that an increase in weight did not necessarily imply a failure of weight loss at the end of the follow-up period. However, a higher initial BMI and older age are independent predictors of subsequent weight regain.

CONCLUSIONS AND PERSONAL CONTRIBUTIONS

In this study, I had as my main objective the evaluation of body composition and bone metabolism after gastric sleeve surgery. The evaluation of these major indicators is critical, given that it is well known that after bariatric surgery, metabolic changes that occur ameliorate existing chronic complications, as well as the fact that there are also undesirable effects, such as changes in bone metabolism resulting in bone loss

I performed retrospective research on a series of patients who had a prospective follow-up, 6 and 12 months after the gastric sleeve intervention. The general structure of the paper contains four studies that will be described below.

In the first part of the thesis, I performed a general characterization of the studied cohort. I have analyzed a number of 323 patients, with an mean age of 41.62±11.04 years, of which 41.18% were men and 58.82% were women. The weight and all anthropometric indices registered significant decreases during the follow-up period. In addition, 12 months after gastric sleeve surgery, more than 67% of patients were no longer classified as obese. A lower preoperative BMI and a younger age were independent predictors of weight loss amount.

I also observed an improvement in all evaluated chronic complications, among which I mention the complete remission of diabetes that was achieved for 63.2% of patients plus a partial remission for another 13.2%.

The results that have been recorded in the case of our group of patients are comparable to those in the specialized literature, the weight loss determined by TWL% and the remission percentage of DM type 2 even reaching the values reported for RYGB. After the surgery, the patients were recommended to supplement with vitamins according to the current guidelines. Compared to the data reported for RYGB, I obtained better results in phospho-calcium metabolism, and the preoperative vitamin D deficiency was less prevalent, a fact explained by the strictly restrictive nature (without malabsorption component) of SG. A particularity of the patients was the low presence of secondary hyperparathyroidism compared to other identified studies.

Although BMI continues to be an essential indicator in the diagnosis and treatment of obesity. Body composition expresses much better the degree of adiposity, the percentage of muscle mass and the phenotype of obesity. Starting from this idea, in the second study I evaluated the changes in body composition parameters and the impact that fat mass and lean mass respectively have on bone mineral density. Similar to other specific studies, the sustained loss of fat mass was inevitably associated with a loss of lean mass as early as the first 6 months after gastric sleeve surgery. Six months after surgery, the decrease in lean mass recorded an average value of 22% of the weight loss, with some individual values even reaching 56%. A lower baseline BMI was observed at the patients who lost more muscle mass, and android-type obesity along with a higher glycemic value were among the predictors of this loss.

The idea of sarcopenic obesity has gained attention during the last few years. In this context, I tried to evaluate, also in the second study, the prevalence of sarcopenia and its evolution after bariatric surgery, by using DEXA measurements. Our searches did not revealed any other similar studies. Moreover, there is no standard for patients who have undergone bariatric surgery. The evaluation becomes complicated by the fact that they start from the obesity category and, as I showed in the first study, more than 67% end up by falling out of this category. Lacking direct measurements of muscle strength as a standardized marker of sarcopenia, I attempted to estimate the prevalence of low lean mass by using several important formulas from the literature with different proposed thresholds. I have obtained very different results depending on the criterion I used, but in all cases the prevalence of low muscle mass was higher in men both preoperatively and postoperatively.

Another important conclusion of the second study was represented by the variation degree of total BMC that depended on the degree of ASMI decrease, a relationship that remained independent of age, sex, or other factors recognized as having a negative impact on bone (DZ, smoking status). Because lean mass loss has been positively correlated with bone loss, maintaining as much muscle mass as possible makes it a potential target in preventing bone loss. At the same time, we observed a more pronounced loss of BMD in the first 6 months, among men, and in the following period, 6-12 months, the decline between the sexes has been similar. Corroborating the two previous results, I conclude that the first period after the bariatric surgery may represent an important therapeutic window in preventing BMD decline, especially in the cases of men.

The relationship between adipose tissue and the skeletal system is also recognized and intensively studied. In the past, the excess of adiposity was considered protective factor for bone, but more recent data have indicated negative effects on the bone. Consistent with these, in my cohort, I have identified a negative relationship between total adipose tissue and BMD when I adjusted the correlation for weight. In addition, the percent body fat correlates negatively with BMD even without adjustments. Thus, we can conclude that excess adiposity has a negative impact on bone, especially when accompanied by reduced lean mass.

In the third study, I deepened the study of the relationship between adiposity and bone, trying to identify the effect of SG on changes in adiponectin and bone markers. Moreover, I aimed to establish some links which represents a foundation of this complex relationship by identifying the role of regional changes in body composition that are a part of this equation.

First of all, I determined the relationship of adiponectin with the regional distribution of adiposity, which I measured by using the "DXA whole-body" method. I observed a negative association with the fat in the android region, while gynoid fat appeared to have a positive effect on adiponectin levels. The relationships held even after complex adjustments for potential confounders. After gastric sleeve intervention, I observed, as expected, increases in adiponectin levels. In exchange, the analysis by which we demonstrated that the reduction of android adiposity leads to the increase of the level of adiponectin, is a relative novelty in the literature on bariatric surgery. The mechanisms by which the change in adiponectin is favored by the decrease in regional adiposity are not yet sufficiently known, and the way in which the gastric sleeve surgery changes the level of adiponectin according to variations in body composition parameters has not been studied.

Bone turnover markers were also increased after the gastric sleeve intervention, with more pronounced bone resorption in the first 6 months, while bone formation reached its maximum value only at 12 months. By calculating the osteocalcin/CTX ratio I showed that, in the first 6 months, the greatest imbalance in bone metabolism is recorded, accompanied by a decoupling of resorption from bone formation, the data showing an attempt to return to the initial balance in the following months.

An important conclusion of this third study is represented by the close connection I have identified between adiponectin and osteocalcin. We identified adiponectin variation as an independent predictor of osteocalcin variation after gastric sleeve. Moreover, we observed that variation in adiponectin is independently related to change in bone mineral density (in women).

The presented analysis is the first one I have identified that takes into account the impact of regional adipose tissue on adiponectin and its relationship with bone markers, an additional novelty factor being that it was performed on patients with gastric sleeve surgery, an intervention that is used and implicitly studied more intense only in recent years.

The fourth study consisted of following changes in body composition parameters and bone mineral density 4 years after the gastric sleeve intervention. In addition, I sought to identify the factors that are associated with the decrease of BMD 4 years post-surgery.

While during the second study, I observed that all the patients lose weight in the first year after gastrectomy, in this study I identified a subsequent weight regain, determined by the increase in fat mass, in parallel with the continuation of the process of losing lean mass. However, I have noticed variations in the evolution of weight and anthropometric indices at the individual level, some patients continued to lose weight after 4 years. In the study group, a higher initial BMI and older age are independent predictors of subsequent weight regain.

Bone loss as represented by the decrease in BMD continued after the first year, with an accelerated rate for those who maintained their weight 4 years after gastric sleeve intervention. A plausible explanation is represented by the protective role on BMD of mechanical (re)loading in patients with weight regain. In patients who maintained their weight at 4 years, decreased BMD was associated with change in ASMI muscle index.

To my knowledge, the present study is the first to analyse long-term body composition changes and their relationship with bone mass loss as a function of weight regain in gastric sleeve patients.

In addition to the personal contributions and the particularities of the previously mentioned studies, I emphasize that the analysis was carried out on the largest batch of patients in Romania who underwent bariatric surgery and were closely monitored and extensively evaluated using body composition parameters over an extended period of time.

Limitations of the study:

• The patients were evaluated only by ``DXA whole body``, I did not have BMD values at the level of the lumbar spine, respectively of the hip.

• Lack of measurement of muscle strength to assess sarcopenia

• Lack of biochemical and hormonal investigations 4 years after bariatric surgery

Future research directions derived from the current study:

• Prospective follow-up of fracture risk in patients from the studied group.

• Performing DXA measurements of the lumbar spine, hip and TBS in patients before and after bariatric surgery

• Developing of a model for evaluating the prevalence of sarcopenia in patients undergoing bariatric surgery.

• The inclusion of some standardized physical exercise recommendations in order to prevent the loss of muscle mass and the monitoring of bone evolution in the period immediately following bariatric surgery (0-6 months).

• Creating a study group of patients with obesity receiving medication with GLP-1 analogues for weight loss, with body composition follow-up.

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1. **Malinici, E**, Sirbu, A, Popa, M, Andrei M., Ioacara S, Copaescu C, Fica S. *Bone Mineral Density Trends During the First Year After Laparoscopic Sleeve Gastrectomy - a Cohort Study on 241 Patients*. *OBES SURG* 31, 4885–4892 (2021). https://doi.org/10.1007/s11695-021-05661-x, (capitol 7) ***Impact Factor-4.1***
    - Articol premiat UEFSCDI cu indicativul premiului: PN-III-P1-1.1- PRECISI-2021- 65895 din data de 2021-10-22 19:30:18
2. **Malinici, Elisabeta**; Sirbu, Anca; Popa, Miruna; and Fica, Simona (2021) *"Linking the brain and bone through fat,"* Journal of Mind and Medical Sciences: Vol. 8: Iss. 1, Article 4. DOI: https://doi.org/10.22543/7674.81.P1726 (capitol 1)

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