Biochemical Modifications Related to Calcium Deficiencies in Obesity and After Laparoscopic Sleeve Gastrectomy

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Lately there is some discussion about an inverse relationship exists between calcium intake and obesity markers such as body weight, weight gain or body fat percentage. However, numerous studies question the idea whether adequate calcium nutrition can prevent or even reduce obesity. However, the disagreement from many studies seems to have more to do with the interpretation of the data than the data itself, with different hypothesis which could be valid in different specific populations. Still, the major finding we present here are in line with previous research demonstrating that lower levels of serum calcium are common after bariatric surgeries.

Keywords: calcium, serum, laparoscopic, gastrectomy

Obesity is a multifactorial disease and is characterized by a positive energy balance that results from excess energy intake, insufficient energy expenditure and it is manifested by an excess of adipose tissue [1]. In the last decades, it has become a major public health problem that increases health care costs, reduces life years and the quality of life [2]. The World Health Organization estimates that, by 2020, 2.3 billion adults will be overweight and more than 700 million will become obese [3]. Furthermore, obesity has a strong correlation with the development of many comorbid conditions such as insulin resistance, type 2 diabetes mellitus, hypertension, dyslipidemia, metabolic syndrome, as well as other associated complications, such as those related to a variety of biological and biochemical modifications (e.g. increased oxidative stress status), some cancers, pain and neuropsychiatric-connected manifestations etc. [4-15]. Such medical conditions were found to be specific also to pediatric patients' populations, making childhood obesity an even more important healthcare issue [16-18].

In the literature there is a hypothesis that an inverse relationship exists between calcium intake and obesity markers such as body weight, weight gain or body fat percentage. However, numerous studies question the idea whether adequate calcium nutrition can prevent or even reduce obesity. The conflicting results have led to a lack of general agreement. Many reviews and meta-analyses have tried to address the apparently contradicting information in an effort to reach a consensus. However, the disagreement may have more to do with the interpretation of the data than the data itself, with different hypothesis which could be valid in different specific populations.

For example, two different studies have showed that a low level of dietary calcium increases the risk of hypertension and insulin resistance syndrome [19, 20]. Another study found that dairy products consumption was inversely proportional to obesity. In this study, each daily serving of a dairy product was associated with 21% lower odds of developing obesity [21].

In regard to observational studies, it is almost invariably shown that an inverse association between the intake of dietary calcium and body fat levels exists, which may suggests that calcium influences energy balance in a positive manner, especially in obese participants [22]. Most calcium intake derives from the consumption of dairy products, and thus it may be speculated that the observed association between calcium and body weight may be confounded by other nutrients found in dairy products, such as protein or bioactive peptides. On the other hand, this association could be due to the fact that individuals who consume a high dairy diet may live a healthier lifestyle or on the contrary, individuals with a low quality diet are more likely to also consume low dairy intakes. To determine whether this association is causal and it is not only a correlation, it is necessary to find the exact mechanisms underlying how calcium influences the energy balance.

One possible explanation on how calcium intake influences the energy balance in human body was proposed by Zemel et al [23]. These authors hypothesized that dietary calcium, via its influence on plasma 1,25-dihydroxyvitamin D3 concentrations, regulates the concentrations of intracellular adipocyte calcium and in this way it regulates fat metabolism in the adipocytes. In addition, a low dietary calcium diet leads to an inhibited lipolysis, and to a decreased fat oxidation. Consequently, a diet low in calcium may lead to weight gain, and a high

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dietary calcium intake may have the opposite effect. Other authors [24] who wanted to test this hypothesis conducted an experiment on two groups (placebo vs. experimental). The participants from the experimental group received 800mg dairy Ca per day for a 5 week period, while the control group received the placebo treatment. The results presented by the authors failed to find any effect of calcium supplementation on fat tissue metabolism. These findings together with other results from different studies [25] seem to provide sufficient evidence to question the hypothesis according to which dietary calcium may play a vital role in human energy balance through a calcium-controlled pathway in the fat tissues.

Therefore, another theory emerged suggesting that the effect of calcium on adipose tissue may appear mainly during calorie restriction periods and only in individuals who consume a low calcium diet on daily basis. In addition, a calcium-deficient diet, which can easily be experienced during a weight loss diet, has been found to lead to hunger, noncompliance, and poor weight-loss outcome [26]. Therefore, a low calcium diet is not only detrimental for all attempts to control body fat, but also it may be most relevant to study its effects during body fat loss phase of an individual, when a difference in appetite and hunger sensations is an vital determinant of compliance and also of the outcome in terms of total body fat lost [27].

Although the data on this subject is still conflicting, there is still good evidence that dietary calcium intake plays an important role in human body-weight regulation. Perhaps future studies should concentrate more on describing the exact mechanism or how calcium-deficient diets can amplify hunger and impair compliance.

In regard to low calcium levels presented by patients after bariatric surgeries, different studies showed that malabsorptive procedures may be considered as a risk factor for developing bone disease [28-30] as a result of altered calcium metabolism and compromised calcium absorption [31-34]. For example some studies have investigated calcium absorption after jejuno-ileal bypass surgery. The results showed that calcium absorption decreased by roughly 50% after this type of surgery [35]. Considering that inadequate calcium intake is common after gastric bypass [36-38], this may also contribute to an altered calcium metabolism and bone loss. The aim of this study is to lead to a better understanding of the extent to which calcium absorption and intakes are decreased after laparoscopic sleeve gastrectomy.

Hormones regulating calcium metabolism are often disturbed in severe obesity, but also after bariatric surgeries. For example serum parathyroid hormone is found to be higher in severely obese subjects when compared with non-obese subjects [39]. As before mentioned this hormone has been also shown to decline in patients who suffer dramatic weight loss [40]. However, surprisingly, the data shows that patients who underwent bariatric surgery present persistently elevated serum parathyroid hormone [41-43]. In addition, other studies on patients after bariatric surgeries present results that confirm a decrease in 25-hydroxy-vitamin D levels [44-46]. Furthermore, the literature shows that serum estrogen levels are typically elevated in severe obese populations [47] and that these levels decrease when the individuals are starting to lose body fat [48, 49]. This hormonal profile may stand behind the disturbed calcium metabolism that occurs after bariatric surgeries [50, 51]. On the other hand, bone regulating hormones in bariatric patients and their relationship to calcium absorption and bone loss has not been broadly studied previously in bariatric patients, despite the proven effectiveness of these procedures [52, 53].

Waist circumference it is known to be a strong marker for health risk, since the abdominal fat distribution is associated with many risk factors such as coronary heart diseases and type 2 diabetes [54, 55]. Furthermore, it has been proven that individuals with a large waist circumference suffer impairments not only in general health but also in the quality of life [56]. However, the main reason why we chose to use sagittal abdominal diameter as the measure of visceral obesity was that, among both men and women, sagittal abdominal diameter was found to have stronger correlations with the risk factors in the metabolic syndrome when compared to other measured anthropometric variables, such as waist circumference, waist-to-hip ratio and body mass index. Furthermore, in the regression analysis of one study, the most important risk factor for coronary heart disease and for the metabolic syndrome was found to be the sagittal abdominal diameter [57].

In addition, Pouliot et al have shown that waist circumference and sagittal abdominal diameter are simple, yet most powerful anthropometric indices of abdominal and visceral adipose tissue accumulation and of cardiovascular risk in men and women [58]. These authors present the mechanism of the proposed link between increased visceral adipose tissue and risk factors for coronary heart disease. This mechanism may be based on the occurrence of elevated concentrations of free fatty acids in blood from the enlarged abdominal fat depots. With a multiscan CT technique the sagittal abdominal diameter at the umbilical level has been shown to predict the amount of visceral adipose tissue [58]. In recent studies [59, 60], sagittal abdominal diameter is measured on CT scans, but in our study it was measured with the patient in a supine position using a simple ruler. We considered that the measurement of sagittal abdominal diameter by this easy method is reproducible and accurate.

Experimental part

This study was conducted on 170 patients, all Romanians, hospitalized for bariatric surgery in the Surgery Service, Sf. Spiridon Clinical Emergency Hospital in Iasi (Romania). Eighty five patients (41 males and 44 females) were recruited to be part of the experimental group. These patients were investigated before and after 1 year following the laparoscopic sleeve gastrectomy. The data obtained from this laparoscopic sleeve gastrectomy group was compared to the data from a control group, which was recruited from the waiting list for laparoscopic sleeve gastrectomy, consisting of 85 patients, 31 males and 54 females. The control group was recruited to match weight, abdominal sagittal diameter (ASD) and serum calcium in relation to the corresponding baseline values in the group who underwent laparoscopic sleeve gastrectomy. The exact characteristics of the population sample used in this study can be seen in table 1.

All patients from the experimental group were prescribed the following supplements as mandatory postoperative care: 1 multivitamin daily; iron (325 mg with B12 and folate) daily; calcium citrate (1800 mg) daily; and fat-soluble vitamin supplements (10,000 IU of vitamin A, 1200 IU of vitamin D, 60 IU of vitamin E, and 300 μg of vitamin K) daily.

Serum calcium levels were measured by atomic absorption spectrophotometry, and the coefficient of variation is <2% for this method [61-63].

Abdominal sagittal diameter, a variable reflecting visceral adipose tissue, was recorded at the umbilical level

as the height (cm) of the abdomen measured from the examination couch.

All patients signed a specific study inclusion agreement annexed to the informed consent form [64], and all experimental biochemical studies were performed in the light of the uniformly accepted ethical principles stated by the Helsinki Declaration [65-70].

Results and discussions

Baseline results

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, ASD or serum calcium concentrations (table 1). However, a statistically significant positive correlation between serum calcium concentrations and ASD was found ($r = 0.227$, $p = 0.003$). None of the patients in this study had any complications during the surgical performance or during the 1-year follow-up period.

Results after 12-months follow-up

Serum calcium concentration decreased significantly in the experimental group, from 9.1 to 8.82 mg/dL ($p = 0.004$), while the exact same trend was observed during the corresponding period in the control group. However, the decrease in the control group was non significant, from 9.0 to 8.93 mg/dL ($p = 0.388$). The intergroup difference in serum calcium concentrations after 12 months post operation ($p = 0.156$) was non significant (fig. 1).

Regarding the abdominal sagittal diameter, in the experimental group, the mean ASD decreased from 29.3 cm at baseline to 22.4 cm, ($p < 0.001$). In the control group, a very small change but non-significant in mean ASD was observed between baseline and 12 months follow-up, 29.5 cm to 29.3 cm, respectively ($p = 0.830$). ASD was significantly different in the two groups at the 12 months follow-up ($p < 0.001$) (fig. 2).

Adjusted analyses - ANCOVA

To find out if any of the post operation variance is explained by the preoperation values we used the analysis of covariance. When we controlled the preoperation values, using ANCOVA, the statistical significance difference between control and experimental groups maintained for ASD after 12 months ($p < 0.001$) and there was still no significant difference for serum calcium levels 12 months post operation ($p = 0.218$).

Our major findings are in line with previous research that demonstrates that lower levels of serum calcium are common after bariatric surgeries [71-75]. Although there are studies that presented no significant change in calcium metabolism after bariatric surgery [76, 77]. Furthermore, there is some evidence suggesting that obesity can be protective against osteoporosis, and when even a moderate weight loss occurs, a decrease in bone mineral density appears [78]. In consequence, with more dramatic weight loss, which is expected to take place after bariatric surgeries, there is an increased risk of low bone mass and metabolic bone disease [79, 80].

As before mentioned, although the exact mechanism by which calcium intake regulates visceral fat is unclear,

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 (±SD). ASD= ABDOMINAL SAGITTAL DIAMETER

	Laparoscopic sleeve gastrectomy group	Control group	Group comparisons (p value)
Gender (male/female)	41/44	31/54	
Age (years)	40.16	42.00	0.098
Weight (kg)	122.00	120.00	0.215
Height (cm)	171.00	169.00	0.276
ASD (cm)	29.30	29.50	0.860
Calcium (mg/dL)	9.10	9.00	0.328

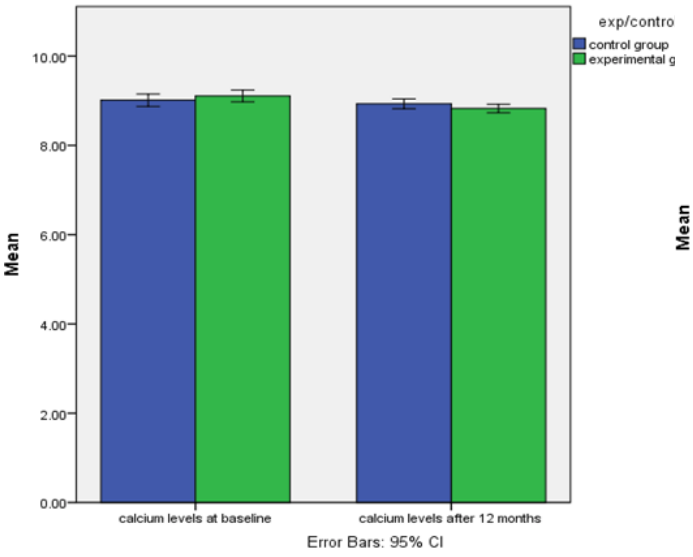

Fig. 1. Changes in serum calcium (mg/dL) from baseline to 1-year follow-up in obese patients treated with laparoscopic sleeve gastrectomy surgery compared to untreated controls.

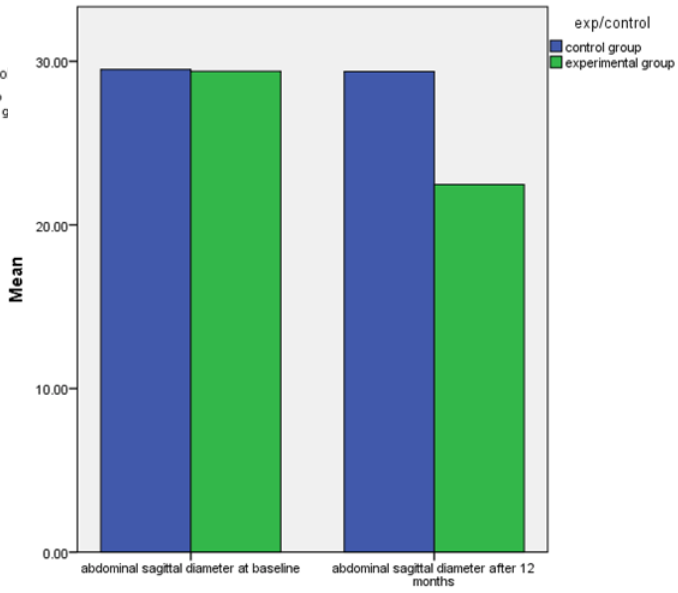

Fig. 2 Changes in ASD (cm) baseline to 1-year follow-up in obese patients treated with laparoscopic sleeve gastrectomy surgery compared to untreated controls

two potential mediators include estrogen and cortisol. Estrogen is associated with less central fat deposition including a lower sagittal abdominal diameter compared to subcutaneous fat deposition [81, 82]. In addition, studies have shown that dietary calcium is associated with the metabolism of estrogens to relatively more active forms [83, 84]. Furthermore cortisol is known to promote intra-abdominal adipose tissue accumulation [85]. It has been suggested that high dietary calcium intake may result in lower cortisol production by inhibiting 1,25-dihydroxyvitamin D3-mediated expression of adipocyte 11-β-hydroxysteroid dehydrogenase type 1, the enzyme that converts cortisone to cortisol [86]. However, the level of calcium intake needed to influence estrogen and cortisol effects on intra-abdominal adipose tissue accumulation and whether this differs by gender or age is not known.

Hypocalcemia is a well-recognized complication of malabsorptive operations, such as laparoscopic sleeve gastrectomy. The results of this study have similarly shown a significant decrease of calcium levels after 12 months. It is very important to note that even if there was a significant decrease in serum calcium levels in the experimental group (from 9.1 to 8.82 mg/dL, $p = 0.004$), the values remained in the normal ranges (8.5-10.2 mg/dL). However, in parallel with the development of hypocalcemia, the incidence of secondary hyperparathyroidism increases with time. That is one of the main reason why postoperative care and long term monitoring is vital.

Furthermore, patient education is a critical component of both preoperative preparation and continual postoperative care. This is already incorporated into the bariatric programs by the surgeons, but it should be handled with the knowledge that nutritional deficiencies are a rare but distinct complication after these operations. The literature presents unambiguous results: despite counseling, the noncompliance showed by patients after bariatric surgery is typically up to 40% [87]. Patient compliance is a major concern after bariatric surgeries especially because surgeons have no control over it. This study reflects the true incidence of calcium deficiency after laparoscopic sleeve gastrectomy surgery performed within a comprehensive bariatric surgery program that involves comprehensive nutritional counseling, monitoring, and supplementation.

Conclusions

Undeniably, malabsorptive bariatric surgeries result in an altered calcium metabolism in some individuals. It is our opinion that these patients need long-term follow-up with frequent evaluations and immediate replacement of these essential nutrients with the help of a better diet or with dietary supplements. The specialized clinics performing these operations as a treatment for morbid obesity need to prepare to follow these patients long-term and to address potential nutrient deficiencies. The programs developed by these clinics should include physical education and nutrition information classes and contribute to a better understanding on how to live a longer healthier lifestyle. Further studies should be conducted to explore the exact incidence of long-term metabolic consequences after bariatric surgeries and what is to be done in order to prevent them.

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