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Research Article

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THE EFFECT OF BARIATRIC SURGERY ON CALCIUM METABOLISM

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Abstract

Objectives: Obesity is one of the most important chronic metabolic diseases that includes many comorbidities. Lifestyle changes play the most important role in the treatment of obesity. Despite this, medical treatment and bariatric surgery procedures gain importance in patients whose weight control can not be achieved. In recent years, sleeve gastrectomy (SG) has become very popular. Nevertheless, its effects on gastrointestinal system physiology and bone metabolism are still not known properly.

Materials and Methods: Fifty-two patients who underwent SG between 2018 and 2019 were included in our observational study. Calcium, albumin, albumin-adjusted calcium (AAC), phosphorus (P), 25-hydroxyvitamin D [25(OH)D], alkaline phosphatase (ALP), parathyroid hormone (PTH), creatinine, glomerular filtration rate (GFR) and body mass index (BMI) of the patients were recorded both in the pre-operative period and three months postoperatively. Patients were grouped as patients with low calcium (10.2mg/dL) according to pre-operative and post-operative calcium levels.

Results: The mean age of the patients was 38.96±8.93 years. 1 (8.33%) out of 12 patients with high serum calcium levels in the pre-operative period had low serum calcium levels in the post-operative period, eight patients (66.67%) had normal reference values, three patients (25%) had high serum calcium levels, the difference was significant. Based on ACC, eight patients (15.38%) had high calcium levels postoperatively.

Conclusion: Hypocalcemia, normocalcemia, and hypercalcemia may be observed during the follow-up after bariatric surgery. Although PTH and 25(OH)D play the most important roles in calcium metabolism, the interaction of bone- gut hormones are still unclear and complicated.

Keywords: Sleeve gastrectomy, hypercalcemia, bone, gastric hormones.

Introduction

Obesity is a serious yet preventable health problem all over the world.[1] Hypertension, cardiovascular diseases (CVDs), Type 2 Diabetes Mellitus, non-alcoholic fatty liver disease (NAFLD/ steatohepatitis), obstructive sleep apnea, cancer, impaired quality of life, depression are the comorbid conditions associated with obesity.[2] Bariatric surgery options could be considered in patients who do not respond to diet, sports or medical treatment. Vitamin D deficiency is common in the obese population. Calcium deficiency may be detected in obese individuals in the pre-operative period.[3] Ionized calcium (Ca^{+2}) is the key to ensuring cell membrane stability, so its level in circulation is tightly maintained. Important changes are present in mineral metabolism in obese patients; firstly, adipose tissue accumulates vitamin D and reduces its use for a substrate of 25(OH)D synthesis. Vitamin D provides intestinal calcium and phosphorus absorption, stimulates bone regeneration, and plays a key role in mineral homeostasis by regulating PTH and Fibroblast Growth Factors-23 (FGF-23) synthesis.[4] It is thought that leptin is the adipokine secreted from adipose tissue that provides the relationship between adipose tissue and the skeletal system. The presence of leptin receptors in osteoblasts and the determination of the effects of leptin on bone suggest that leptin works together with PTH, $1,25(OH)_2D_3$, FGF-23. Leptin, PTH, FGF-23 and bone alkaline phosphatase were found in higher levels in a study on female patients having undergone bariatric surgery.[5] As the frequency of bariatric surgery has increased, publications on its effects on bone health also increase. In our study, we detected patients who developed hypercalcemia after sleeve gastrectomy (SG) and examined the effects of SG on calcium metabolism from a detailed perspective.

Materials and Methods

Fifty-two patients having undergone sleeve gastrectomy (SG) between 2018- 2019 were included in our observational study. All the patients had to meet the criteria for bariatric surgery bearing a BMI of ≥40 kg/m^2 or a BMI of ≥35 kg/m^2 with obesity-related complications such as poorly controlled Type 2 Diabetes Mellitus and hypertension. Exclusion criteria included that chronic kidney disease, solid and hematological malignancies, thyroid dysfunctions, thiazide diuretics medications. Calcium, albumin, albumin-corrected calcium (ACC), phosphorus (P), 25(OH)D, alkaline phosphatase (ALP), parathyroid hormone (PTH), creatinine, glomerular filtration rate (GFR) and body mass index (BMI, kg/m^2) of the patients were recorded in the pre-operative period and three months postoperatively. ACC was calculated with the formula [(4- serum albumin concentration in g/dl) * 0.8) + total serum calcium (mg/dl)].

Statistical analysis

Continuous variables were expressed as mean ± standard deviation and categorical data as numbers and percentages. In the intergroup analysis of continuous variables, normality analyzes were performed with the Kolmogorov-Smirnov Goodness of Fit Test. Preoperative-postoperative analyses of continuous variables with normal distribution were performed with the Paired Samples T-test and those that did not fit with the Wilcoxon Signed Ranks Test. The McNemar test was used for preoperative-postoperative comparison of categorical data. Data were analyzed using IBM SPSS Statistics 22.0 (IBM Corporation, Armonk, NY, USA) packaged software. The value of $P < 0.05$ was considered statistically significant.

Results

The mean age of the patients was 38.96±8.93 years, 92.30% of whom were female. 10 patients (100%) with a low (<8.4 mg/dL) preoperative serum calcium level reached normal reference values (8.4-10.2 mg/dL) in the postoperative period. 23 of them (76.7%) had normal and 6 (20%) had high (>10.2 mg/dL) serum calcium levels. 1 (8.3%) out of 12 patients with high serum calcium levels in the pre-operative period had low serum calcium levels in the post-operative period, eight patients (66.70%) had normal reference values, three patients (25.00%) had high serum calcium levels, the difference was significant (Table 1).

Based on corrected calcium level (ACC); it was determined that 11 patients with high ACC levels in the post-operative period. Among them, while eight patients (15.40%) had normal ACC levels preoperatively, two patients (18.20%) were found to have high serum calcium levels preoperatively and postoperatively (Table 2).

In the post-operative period, the mean BMI (34.36±6.28) decreased statistically ($p<0.05$) compared to the pre-operative period (47.36±6.38), on the other hand, serum P, 25(OH)D, ALP, albumin, PTH, creatinine and GFR levels were not found to be statistically significant ($p>0.05$) (Table 3).

Evaluation of pre-operative and post-operative values of 8 patients with high post-operative ACC is shown in Figure 1.

Table 1. Calcium levels three months after bariatric surgery

		Pre-operative serum calcium			Total	*P*
		<8.4 mg/dL	8.4-10.2 mg/dL	>10.2 mg/dL		
Post-operative serum calcium	**<8.4mg/dL**	0 (0%)	1 (3.33%)	1 (8.33%)	2 (3.85%)	**0.034***
	8.4-10.2 mg/dL	10 (100%)	23 (76.67%)	8 (66.67%)	41 (78.85%)	
	>10.2mg/dL	0 (0%)	6 (20.00%)	3 (25.00%)	9 (17.31%)	
Total		10 (100%)	30 (100%)	12 (100%)	52 (100%)	

* McNemar Test (Column percentages are shown)

Table 2. ACC levels before and three months after bariatric surgery

		Pre-operative ACC			Total	*P*
		<8.4mg/dL	8.4-10.2mg/dL	>10.2mg/dL		
Post-operative ACC	**<8.4mg/dL**	1 (7.69%)	1 (3.57%)	1 (9.09%)	3 (5.77%)	**0.014***
	8.4-10.2mg/dL	12 (92.31%)	21 (75.00%)	8 (72.72%)	41 (78.85%)	
	>10.2mg/dL	0 (0%)	6 (21.43%)	2 (18.18%)	8 (15.38%)	
Total		13 (100%)	28 (100%)	11 (100%)	52 (100%)	

* McNemar Test, ACC: albumin-corrected calcium (Column percentages are shown)

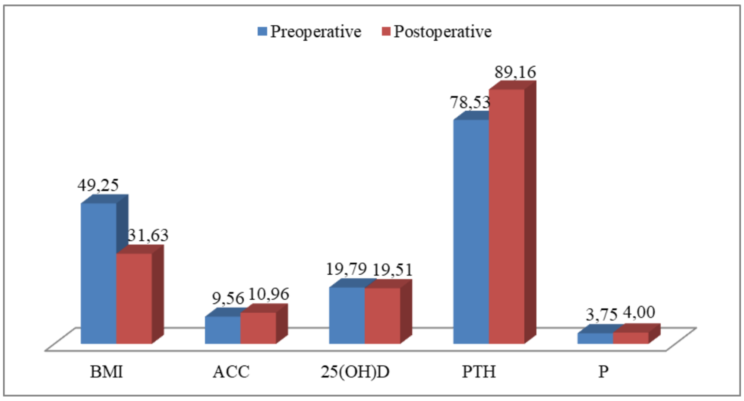

Figure 1. Evaluation of pre-operative and post-operative values of 8 patients with post-operative high ACC (>10.2 mg/dL)

(BMI: body mass index, ACC: albumin-corrected calcium, PTH: parathyroid hormone, P: phosphorus)

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Table 3. Biochemical parameters before and three months after bariatric surgery

	Pre-operative	Post-operative	*P*
BMI (kg/m²) (mean±SD)	47,36±6,38	34,36±6,28	**<0.001***
Calcium((mg/dL) (mean±SD)	9,41±1,08	9,47±0,89	0.711*
ACC (mg/dL) (mean±SD)	9,28±1,13	9,40±0,86	0.470*
P (mg/dL) (mean±SD)	3,92±0,39	3,92±0,33	1.000*
25(OH)D (ng/mL) (mean±SD)	20,62±10,64	21,35±8,05	0.610*
ALP (U/L) (mean±SD)	63,40±28,08	59,98±20,31	0.329*
Albumin (g/dL) (mean±SD)	4,16±0,36	4,08±0,29	0.160*
PTH (pg/mL) (mean±SD)	73,15±24,72	67,03±30,28	0.196*
Creatinine(mg/dL) [median (min-max)]	0.70 (0.50-6.00)	0.75 (0.50-1.10)	0.460**
GFR (ml/dk) [median (min-max)]	97.0 (49.0-121.0)	97.0 (83.9-120.2)	0.926**

* Paired Samples T Test
** Wilcoxon Signed Ranks Test
(BMI: body mass index, ACC: albumin-corrected calcium, P: phosphorus, ALP: alkaline phosphatase, PTH: parathyroid hormone, GFR: glomerular filtration rate)

Discussion

We analyzed the calcium levels of 52 patients who had undergone SG operation due to obesity in the pre-operative period and at the third month postoperatively. The prevalence of post-operative hypercalcemia was calculated as 15.40%. When we evaluated the pre-operative and post-operative values of 8 patients, we saw that the vitamin D levels remained the same despite the elevation of calcium (Figure 1). We aimed to examine the effects of SG on calcium and bone metabolism and the mechanism of hypercalcemia occurrence. As to our knowledge, it is the first publication in the literature on hypercalcemia without parathyroid adenoma after bariatric surgery; we hope that our paper can help in lightening these complex mechanisms like part of the puzzle.

The metabolic effects of bariatric surgery and especially its effects on bone have been examined in recent years. Bariatric surgery is a metabolic procedure that includes both malabsorptive and complex physiological changes.[6] Vitamin D deficiency which is especially common in obese individuals because of accumulation in adipose tissue, may increase further in the post-operative period. Pre-operative PTH elevation is possible and similar to primary hyperparathyroidism. The catabolic effect of parathormone on cortical bone has also been demonstrated in obese individuals by quantitative CT (pQCT).[7] In our study, the mean 25(OH)D level of the patients was 20.62±10.64ng/mL, PTH levels were 73.15±24.72pg/mL. In order to decide whether secondary hyperparathyroidism has developed or the patient has primary hyperparathyroidism, it is important to measure calcium, albumin and PTH in the pre-operative period. For musculoskeletal health, reduction of fracture risk, preservation of bone mineral density, and prevention of secondary hyperparathyroidism after SG, 25OHD levels are recommended to be above 75nmol/L, 2000-4000 IU/day (at least 3000IU/day) vitamin D3, 1200-1500 mg/daily calcium treatment is recommended.[8,] Vitamin D supplementation was performed at their commended doses in the pre-operative and post-operative periods for the patients enrolled in the study. Bariatric surgery procedures involve both malabsorption and dietary restrictions. Among the causes of vitamin D deficiency in patients after bariatric surgery are; vitamin D deficiency before surgical procedure, insufficient vitamin D support during rapid weight loss after bariatric surgery, bile salt deficiency associated with bariatric surgical procedures, vitamin D malabsorption due to intestinal bacterial overgrowth.[9] Osteomalacia cases with severe bone pain secondary to calcium and vitamin D deficiency after bariatric surgery are also encountered. Calcium and 25(OH)D levels should also be measured during replacement. Suthakaran et al. found increased calcium values within the normal reference range 24 months after RYGB and SG. They thought that it was associated with post-operative temporary 25(OH)D elevation and vitamin supplementation.[10] No significant changes in post-operative 25(OH)D levels were observed in our study. There was a significant decrease in BMI of the patients in the pre-operative (47.36±6.38) and post-operative period (34.36±6.28). Hormonal change that causes bone loss due to calorie restriction involves cortisol, adiponectin, 25(OH)D, ghrelin increases, Insulin-like Growth Factor-1 (IGF-1), estrogen, leptin, glucagon-like peptide-1 (GLP-1), GLP-2, Gastric inhibitory polypeptide (GİP), IL-6, and tumor necrosis factor (TNF) alpha decreases.[11] Studies show increased leptin and IGF-1 levels after bariatric surgery.[12] After SG, ghrelin and leptin decreases, adiponectin, GLP-1 and PYY levels also increase. GH response improves after bariatric surgery.[13] Negative regulatory effects on osteoblastic bone formation PYY and the anabolic effect of ghrelin have been shown in studies.[14,15]

Calcium absorption is expected to be better in the duodenum and jejunum due to the low pH, while it is absorbed in greater amounts due to a longer stay in the ileum. As a result, 65% of calcium absorption is achieved. There are two epithelial calcium channels that support the passive transport of Ca^{+2} from the apical membrane to the enterocyte cytoplasm; transient receptor potential vanilloid 5 (TRPV5) and TRPV6. The largest store of calcium in the body is bone. Therefore, it is important in bone calcium homeostasis. Normal serum calcium levels can be maintained by increased levels of $1,25(OH)_2D_3$ and PTH. While vitamin D receptor (VDR) signaling in osteoprogenitors increases Receptor Activator of Nuclear Factor κB (RANKL) expression, VDR signaling in mature osteoblasts has anabolic effects by reducing RANKL expression. The main effect of $1,25(OH)_2D_3$ and VDR is calcium absorption in the intestine. Only 8-10% of calcium absorption takes place in the duodenum.

In a study designed with three groups of patients, i.e., who underwent Roux-en-Y gastric bypass (RYGB) and SG or obese but non-operated patients had been followed up in terms of fracture risk for three years. They found that the fracture risk of those who had RYGP was similar to obese patients who were not operated and that there was a decrease in fracture risk in patients who had SG.[16] In a retrospective cohort analysis of 49113 bariatric surgery patients (16371 having undergone RYGB, 16371 having undergone SG a significantly reduced risk of humeral fracture and the overall fracture was found in those who had undergone SG.[17] In the first study comparing the bone mineral density (BMD) of adolescent and young adults having undergone SG with patients who were followed-up without surgery, a decrease in the femoral neck and total hip BMD and an increase in cortical volumetric BMD in both regions were found after surgery.[18] Stemmer et al. revealed a tendency for higher bone resorption and lower bone formation in rats administered RYGB in their animal study. IGF-1 was found to be low in rats treated with SG, but it was much lower in those treated with RYGB. In their study, they found that RYGB, but not SG, caused a significant trabecular bone loss that could not be corrected by dietary supplementation. In this study, similar weight loss in both sex groups includes the effect of mechanical factors and highlights the effect of endocrine and hormonal factors. A similar decrease in leptin insulin levels, a similar increase in postprandial GIP levels, and gastric pHs were detected. Low albumin level, decreased lipid absorption, and mild decrease in calcium was detected only after RYGB.[19] Saif et al. did not detect changes in calcium, magnesium and phosphorus levels in the first, third and fifth years of follow-up after SG in their studies, but it was observed that the magnesium level increased significantly from baseline. In the first year follow-up of the patients, PTH and 25(OH)D levels returned to normal levels with replacement therapy. However, despite vitamin D replacement, the level remained low in 33% of patients. PTH levels were elevated at five years, although there was no change in 25(OH)D levels.[20]

After SG, ghrelin levels decrease by removing the gastric fundus where ghrelin is most abundant, GLP-1, GLP-2, peptide YY (PYY), cholecystokinin levels increase, thus increasing the feeling of satiety. In malabsorptive procedures such as RYGB, they found an increase in the risk of fracture in osteoporotic regions that occur 2-5 years after the operation, but no such result with SG was achieved. In some studies, it has been thought that bone marrow adipose tissue (BMAT) may contribute to the negative effects on the skeletal system after bariatric surgery.[21,22] BMAT is an endocrine organ that accounts for 70% of the bone marrow volume and 10% of the total fat mass in healthy adults. As a defense mechanism in starvation states, the bone marrow can accumulate adipose tissue or secrete adipokines such as adiponectin, which can increase insulin sensitivity and increase appetite. The relationship between bone marrow adipose tissue and BMD is still unclear.[23,24] Cawthorn et al. showed that BMAT expansion in caloric restriction is an endocrine organ with systemic effects with increased circulating serum adiponectin level.[25] We think that the effects of BMAT on calcium and bone metabolism secondary to weight loss after bariatric surgery are subjects that need to be investigated.

There are publications mentioning that leptin increases the level of osteocalcin, a hormone produced by osteoblasts and known to play a role in bone growth and glucose-insulin homeostasis recently. Studies have shown that leptin stimulates osteocalcin release through its receptors in the hypothalamus. Thus, leptin has beneficial effects on the skeletal system and energy homeostasis.[26] Osteoblasts and adipocytes are cells originating from the same mesenchymal progenitor that play an important role in bone remodeling. 25(OH)D is a key molecule in mineral homeostasis in bone remodeling due to its main effect on increasing intestinal calcium and phosphorus absorption and regulating PTH and FGF-23 synthesis. Leptin is the molecule that transmits signals from adipose tissue to bone, and osteocalcin is just the opposite. Adipose tissue stores cholecalciferol, which can affect calcium balance and energy expenditure.[4,27] FGF-19 level, which is low in obese patients, has been shown to increase after bariatric surgery. On the contrary, FGF-21 level is high in obese patients; it has been shown to decrease after SG, but not after RYGB.[28] Arhire et al. found an increase in adiponectin and a decrease in leptin after SG. Although there was no decrease in BMD, they detected an increase in bone mineral content (BMC) one year after the operation.[29] It should be kept in mind that parathyroid adenoma may develop secondary to hypocalcemia after bariatric surgery.[30] Parathyroid adenoma was not clinically considered and detected in our patients with hypercalcemia.

The limitation of our study is the lack of long-term calcium follow-up. However, this is the first article in the literature on this subject. With the rapid increase in obesity worldwide, the increase in the frequency of bariatric surgery and the mechanisms of osteoporosis after bariatric surgery are still being investigated. Based on the fact that SG does not increase the risk of fracture and on the findings of post-operative hypercalcemia in our study, issues such as the effects of bone marrow adipose tissue the interaction of hormones secreted from the intestine with the bone should be clarified and further studies are needed.

Ethical Considerations: The protocol was conducted in agreement with the Helsinki Declaration. We obtained informed consent from all participants before their participation. The ethics committee approval was obtained from the Keçiören Training and Research Hospital Observational Research Ethics Committee (Ethics Committee Approval No:2012-KAEK-15/2484).

Conflict of Interest: The authors declare no conflict of interest.

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